Exhibit E

Polymer Science and Materials Chemistry

Exponent®

Expert Report of Dr. Steven MacLean

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

No. 2:12-MD-02327
MDL 2327

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Limitations

At the request of Butler Snow LLP, Exponent reviewed relevant scientific literature, historic documented studies and expert reports for the pending litigation. Exponent investigated specific issues relevant to this report as requested by the client. The scope of services performed during this investigation may not adequately address the needs of other users of this report, and any reuse of this report or its findings, conclusions, or recommendations is at the sole risk of the user. The opinions and comments formulated during this investigation are based on observations and information available at the time of the investigation.

The findings presented herein are made to a reasonable degree of scientific and engineering certainty. We have endeavored to be accurate and complete in our assignment. If new data becomes available, or there are perceived omissions or misstatements in this report, we ask that they are brought to our attention as soon as possible so that we have the opportunity to address them.

Steven MacLean, Ph.D., P.E. Biography

I am a Principal Engineer in the Polymer Science and Materials Chemistry Practice at Exponent Failure Analysis Associates, Inc. ("Exponent"). My expertise and experience includes the chemical and physical behavior of polymeric materials in end-use applications, specifically in the evaluation of polymeric components in product safety assessments and product failure analysis. I have a B.S. and M.E. in Mechanical Engineering from Rensselaer Polytechnic Institute, and a M.S. in Material Science and Engineering from Rochester Institute of Technology. I also obtained a Ph.D. in Material Science from the University of Rochester in 2007. I am a registered Professional Engineer in New York and Maryland, a Senior Member of the Society of Plastics Engineers (SPE), and a board member of SPE's Failure Analysis and Prevention Special Interest Group.

During the pursuit of my advanced degrees in materials science, my chosen field of study was polymer science and engineering. Graduate courses taken during my academic career that specifically focused on polymers included, but were not limited to, polymer science, organic polymer chemistry, polymer physics, polymer rheology, polymer processing, bulk physical properties of polymers, adhesion theory, and analytical techniques for polymeric materials. Supplemental course work included mechanics of materials, fracture mechanics, thermodynamics of materials and electron microscopy practicum. At the master's degree level, my polymer research included characterizing the changes in chemical and physical properties of polycarbonate due to multiple heat histories from processing. At the doctoral level, my polymer research was focused on developing and investigating novel formulations of rubber-toughened polyphenylene ether polymers for use in pressurized, potable water systems. The primary emphasis of my dissertation included quantifying changes in select mechanical properties, including fracture toughness and tensile properties, due to the degrading effects from persistent exposure to chlorinated water at elevated temperatures.

In addition to my academic education and training, I have also been actively practicing in the field of polymer science and engineering for the past 20 years. Throughout that time, I have

routinely utilized numerous polymer characterization techniques including, but not limited to, infrared spectroscopy, chromatography, mass spectrometry, and calorimetry as well as optical, scanning electron and transmission electron microscopy. In particular, I have used these microscopic techniques to examine the topography and morphology of fracture surfaces created as a result of polymer cracking. I have also employed these techniques to characterize modes of polymer failure such as creep, fatigue, stress overload and environmentally-assisted stress cracking. In many instances, I have published the use of these analytical techniques to investigate polymer failures in commercialized products in peer-reviewed journal articles and scientific conference proceedings.

Prior to joining Exponent in 2011, I worked for over 15 years at General Electric Plastics (GE) and SABIC Innovative Plastics (SABIC) in a variety of technical roles of increasing responsibilities. Throughout my tenure, I was routinely involved in material selection, performance and testing for, among other things, high-demand applications, product safety assessments, and product failure analysis. As a result I have significant expertise and experience with industry standards and applicable regulations that prescribe the technical performance of polymeric materials in end-use applications, including those in the medical device industry.

At GE Plastics, I was trained extensively in the Six Sigma quality process, and became certified as a Six Sigma Black Belt. As a Certified Six Sigma Black Belt, my responsibilities included improving business processes by employing a variety of well-established statistical methods as well as mentoring and training Six Sigma Green Belts throughout the company.

Throughout my career, I have evaluated the suitability and performance of polymeric materials in end-use applications, including specifically, for the medical device industry. While at GE and SABIC, I worked with numerous medical device companies on material development, material specification, design and manufacturing for a wide variety of medical device applications. These efforts included, inter alia, developing and implementing tests related to the bulk physical properties of polymeric materials specified in said devices as well as material formulation development to meet unique device requirements that could not be met with off-the-shelf grades

of resin. Formulation development often included the selection and refinement of base polymers or alloys, molecular weight, additives, stabilizers, processing aides, lubricants, colorants and inorganic fibers and fillers. In addition to proactive design and material selection assistance, I have worked on hundreds of product safety assessments and failure analyses involving polymeric materials, many of which were performed on medical devices and components.

In my prior role as Director of Global Agency Relations and Product Safety at GE/SABIC, part of my leadership responsibilities included being an active member of the business' Healthcare Resins Advisory Board. The board developed internal processes and standards for the specification, use and sale of GE/SABIC resins in medical device applications. These efforts included ensuring that commercial resin grades within the GE/SABIC healthcare portfolio were assessed for biocompatibility using industry accepted test protocols such as United States Pharmacopeia (USP) Class VI, Tripartite Biocompatibility Guidance, or ISO 10993 Biological Evaluation of Medical Devices standards. For the past several decades, the latter two standards have been supported by the Food and Drug Administration (FDA) and commonly employed to assess the potential for cytotoxicity, hemolysis, pyrogenicity, sensitization issues, among other biological effects, when the human body is exposed to foreign materials. In addition, the board also ensured that "good manufacturing processes" were globally implemented to maximize the purity levels of all compounded materials within the healthcare resin portfolio.

In addition to my relevant training, education and industry experience, I have also reviewed and synthesized the available public literature pertaining to *in vivo* and *in vitro* studies of polymeric mesh devices, long-term implantation of polymeric medical devices, foreign body response to implantable materials, as well as select plaintiff reports which allege *in vivo* PROLENE mesh degradation. A complete list of the reviewed literature can be found in Appendix D.

Polypropylene

Chemical Structure of Polypropylene

Polypropylene is a widely produced polymer which possesses an excellent balance of physical properties, processability, and cost-effectiveness, and is commonly specified for use in a wide range of commercial applications.[1] Polypropylene is formed via a polymerization reaction where propylene molecules (monomers) are combined together in a step-wise fashion to ultimately form linear, chain-like macromolecules (Figure 1A). Polymerization is achieved through breaking the unsaturated (double) bond in propylene, and covalently reacting this bond with the polymer chain. In the current day commercial production of polypropylene, Ziegler-Natta or metallocene catalysts facilitate this reaction.[1] Polypropylene is most commonly produced as a linear polymer (Figure 1B), meaning that the propylene monomers bond to the polymer at the end of the polymer chain, as opposed to forming a branching molecular architecture.[1]

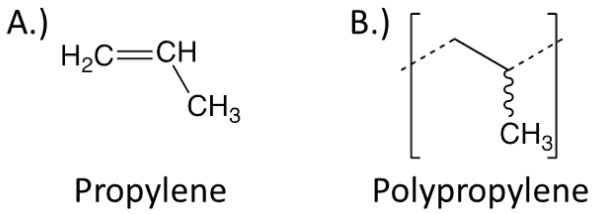

Figure 1. A.) Chemical structure of propylene and B.) Generalized chemical structure of linear polypropylene.

Polypropylene is a vinyl polymer with a lone pendant methyl group in its repeat unit as shown in Figure 1B. Chain growth using these catalysts is designed to attach in a head-to-tail manner such that the pendant methyl groups are regularly spaced.[1] The collective orientation of these groups with respect to the backbone of the polymer, known as stereoregularity, can affect the

[1] Maier, C., Calafut, T. *Polypropylene: The Definitive User's Guide and Databook*. Norwich, NY: Plastics Design Library, 1998.

final physical properties of the polymer.[1,2] As shown in Figure 2, the pendant methyl groups can be oriented in two different directions with respect to the polymer backbone, allowing polypropylene to be produced in three different stereoregular conformations: isotactic (pendant methyl groups along the same side), syndiotactic (alternating sides), or atactic (random orientation). Control over which type of stereoregularity the polymer adopts is determined primarily by the choice of catalyst.[1,2] The majority of commercial polypropylene is manufactured in the isotactic conformation (*iso*-polypropylene).[1]

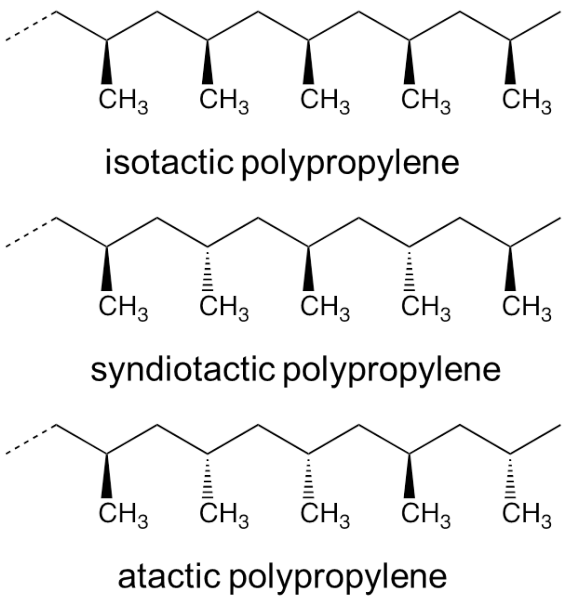

Figure 2. The three most common stereoregular conformations of polypropylene, isotactic (top), syndiotactic (middle), and atactic (bottom).

Crystallinity

Polypropylene is semi-crystalline in nature, meaning that both amorphous and crystalline regions are present throughout the polymer matrix. A typical range for the degree of crystallinity is 20% to 40% for commercially available *iso*-polypropylene.[3] The degree of crystallinity of the product is mainly determined by the stereoregularity and processing conditions. Isotactic

[2] Odian, G. G. *Principles of polymerization*, 4th ed.; Wiley-Interscience: Hoboken, N.J, 2004.

[3] Sastri, V. R. "Commodity Thermoplastics." *Plastics in Medical Devices*. Elsevier, 2014.

polypropylene (*iso*-polypropylene) is the most crystalline conformation, due to the collective orientation of the pendant groups in the same direction allowing for neighboring polymer molecules to align and form a compact, ordered structure. The degree of crystallinity achieved by the material in its solid state directly influences bulk physical and thermodynamic properties.[1] With regard to expected mechanical properties, a higher crystallinity generally results in increased stiffness, yield stress, Young's modulus, and flexural strength among others, but a decreased toughness and impact strength.[1]

Molecular Weight

During synthesis, propylene monomers are converted into polypropylene macromolecules of differing lengths. The lengths of polymeric chains are defined by the number average (M_n) and weight average (M_w) molecular weights. Typical M_w values for commercial polypropylene vary from 220,000–700,000 g/mol[1] depending on a number of variables including the specific catalyst used.

Since there is a degree of randomness associated with the synthesis of most commercial polymers, the total number of monomeric units contained within each polymer chain will vary within a given sample. This range of polymer chain lengths is referred to as the molecular weight distribution (MWD) and is commonly reported as the polydispersity index (PDI). The PDI of a polymer is defined as the quotient of M_w and M_n (M_w/M_n) and is a measure of the broadness of the MWD, with a larger PDI corresponding to a broader MWD. Typical PDI values range from 2.1–11.0 for commercial polypropylene.[1]

Molecular weight and MWD directly influence the mechanical properties and processability of the bulk polymer.[1] Polypropylene resins with a larger PDI are more shear sensitive, meaning the apparent melt viscosity decreases at a faster rate with increasing shear rate.

Thermal Properties of Polypropylene

Thermoplastic materials, including all variants of polypropylene, possess thermal transition temperatures that characterize the thermodynamic behavior of the polymer. These thermodynamic transitions are primarily based on the unique molecular structure and order of a specific polymer. The first of such thermal properties is the glass transition temperature, T_g, which is the temperature at which a polymer shifts from its glassy (more solid-like) phase to its rubbery phase. Typical T_g values for polypropylene range from -35 to 26°C.[1]

The temperature at which crystalline domains are destroyed is known as the polymer's melting point (T_m). Once T_m has been eclipsed, the material's viscosity is sharply reduced and has the ability to readily flow in the presence of driving forces such as pressure or stress. Melting points for polypropylene can vary from 171°C for perfectly isotactic polypropylene to 130°C for syndiotactic polypropylene.[1] In practice, commercially produced *iso*-polypropylene typically melts between 160–166°C due to small regions of atacticity (i.e. noncrystallinity).[1]

Manufacturing of Polypropylene Resins

Industrial synthesis of bulk polypropylene is generally performed using either a bulk slurry (e.g. the Borstar® process or the Spheripol® process), or a gas phase reaction with a solid catalyst bed (e.g. Novolen®, Unipol® PP processes).[4,5] Depending on its end use, the polypropylene resins are then mixed with additives and stabilizers to aid in processing, provide color, enhance mechanical properties, or combat thermal or oxidative degradation. These additional formulation ingredients can be compounded into the finished polypropylene product either in batch mixing, or through continuous mixing (e.g. extrusion).

[4] "*Process Analytics in Polypropylene (PP) Plants*", Siemens AG; 2007, pp:1-9.

[5] Mei, G.; Herben, P.; Cagnani, C.; Mazzucco A. *The Spherizone Process: A New PP Manufacturing Platform*, Macromol. Symp. 2006, 245–246, 677–680.

Processing of Polypropylene Fibers

Polypropylene has melt flow properties that make it well suited for the production of synthetic fibers.[1] Polypropylene fibers are commonly produced via melt spinning, where the polypropylene is melted and extruded through a spinneret followed by cooling and solidification.[1] The process of drawing a polypropylene fiber from the melt exerts uniaxial force on the polymer chains which, after cooling and solidification, results in the polymer chains being preferentially oriented along the drawing axis (i.e. the fiber length). Therefore, the crystalline character in polypropylene fibers is not only dependent on the rate of cooling during melt spinning but also on the induced molecular orientation from the mechanical drawing process.[6]

Polypropylene Applications

Numerous grades of resin with varying properties make polypropylene useful in a wide array of applications including components and devices for the medical industry, injection molded parts for the automotive industry, and other consumer products.[1] Its ubiquitous specification and use is largely due to its excellent balance of bulk physical properties, ease of processing, chemical resistance, and ability to withstand moderate to elevated thermal environments.[1] In addition, polypropylene is generally unaffected when in contact with most solvents, acids, bases, disinfectants, and other common chemicals, which make it an excellent candidate material for many industries, including medical applications.[3]

Polypropylene has found use in numerous applications, including medical devices, textiles, vehicle components and packaging.[1] Polypropylene also finds wide usage in small medical equipment, mainly in hypodermic syringes,[3] but also in medical tubing, trays, sutures, vials and many others. The widespread use of polypropylene in the medical industry stems from its chemical resistance, mechanical strength, biocompatibility, ability to be sterilized, colorability and clarity.[3] As a result, it has become a common material substitution for glass and other

[6] Salem, D. R. *Structure Formation in Polymeric Fibers*. Munich : Cincinnati: Hanser Gardner Publications, 2001.

polymeric materials in the medical industry. Specifically in the case of sutures, polypropylene fibers are now a common material choice because of these desirable properties.[3]

Chemistry of Oxidation and Formaldehyde Fixation

Oxidation of Polypropylene

Despite its semi-crystalline nature, polypropylene, in its neat form, can be susceptible to oxidation in its amorphous regions. Specifically, oxidation occurs at the pendant methyl groups present on the polymer backbone.[1] Polypropylene can oxidize as a result of exposure to heat, oxygen in the air, acidic and basic environments, radiation and UV light.[1,7,8] The energy associated with any of these environments has the potential to break the bonds between a tertiary carbon atom and a neighboring hydrogen atom, resulting in the formation of radicals. These radicals are generally reactive and, in the presence of oxygen, can form hydroperoxides that eventually lead to the formation of carbonyl groups in the form of carboxylic acids, lactones, aldehydes, and esters (Figure 3).[1,9]

[7] Rosato, D. V., Mattia, D. P., Rosato, D. V. *Designing with Plastics and Composites: A Handbook*. Boston, MA: Springer US, 1991.

[8] Wieslawa Urbaniak-Domagala. *The Use of the Spectrometric Technique FTIR-ATR to Examine the Polymers Surface.* INTECH Open Access Publisher, 2012.

[9] Gijsman, P., Hennekens, J., Vincent, J. The Mechanism of the Low-Temperature Oxidation of Polypropylene. *Polym. Degrad. Stab.*, (1993) 42(1):95–105.

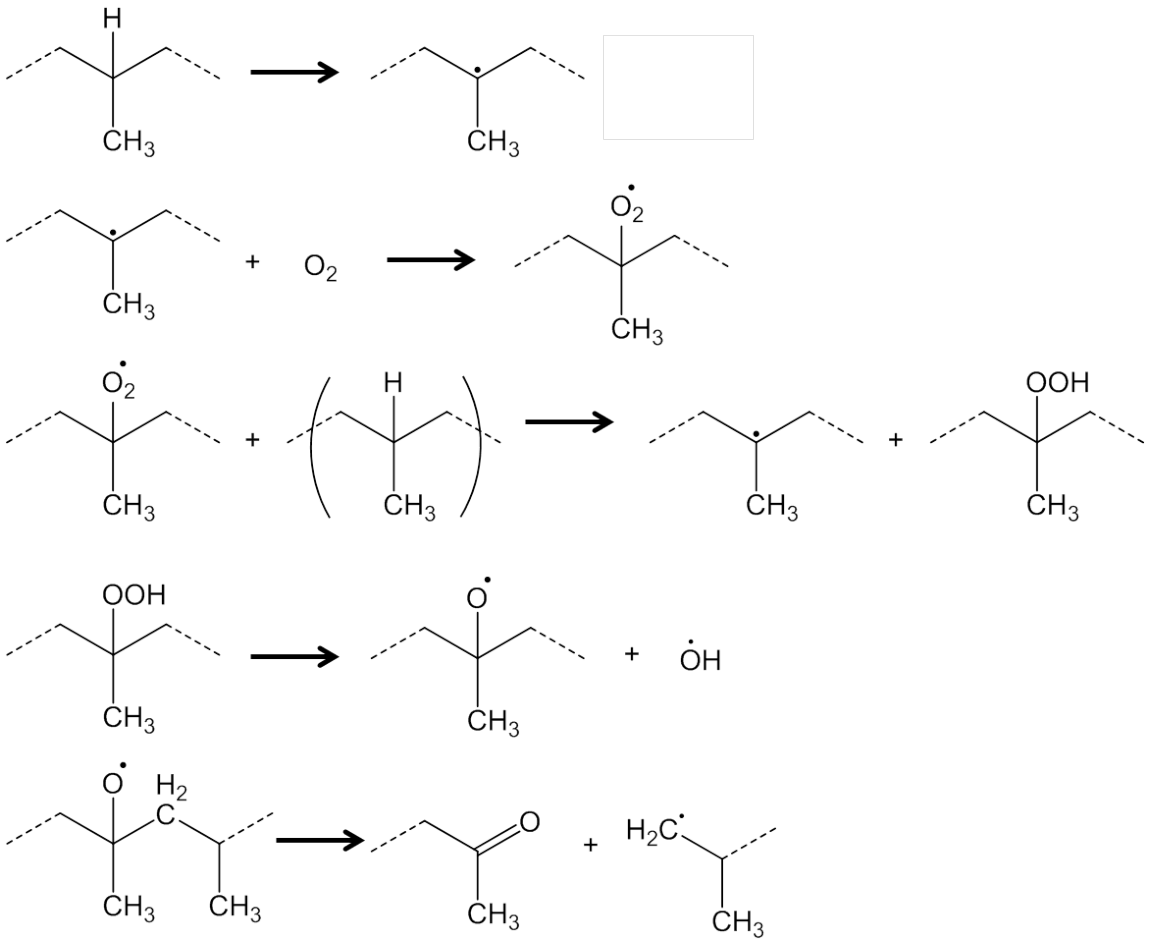

Figure 3. Reported oxidation reaction pathway of polypropylene.[9]

As a result of oxidation, chemical, physical, and mechanical changes may occur in polypropylene. The potential chemical changes consist not only of the formation of carbonyl containing groups, but also a loss in average molecular weight and shifts in molecular weight distribution. Radicals formed during the oxidation process in polypropylene can lead to chain scission resulting in a reduction in molecular weight.[1] Oxidation in polypropylene can also change the physical properties and appearance of the polymer. Polypropylene can turn "yellow-brown" in color and start to "flake away" after it begins to become oxidized.[10] Furthermore, the

[10] *Additives: Antioxidants*. Equistar. p:1–2.

mechanical properties can also change as polypropylene becomes oxidized.[11] In general, it becomes more brittle as evidenced by a reduction in its elongation-at-break (ductility) during tensile testing.

In virtually all engineering applications, antioxidants are used to combat oxidation in polypropylene. These antioxidants are chemical additives which are added to the resin prior to processing and are typically divided into two groups known as primary and secondary antioxidants. Primary antioxidants are radical scavengers which are typically hindered phenolics and secondary aromatic amines.[1,10] These additives react with radicals and hydroperoxides in the polypropylene, thus eliminating the radicals from the polymer. The result is primary antioxidant species containing radicals, which are more stable than the polypropylene radical. Secondary antioxidants are peroxide decomposers which are typically phosphites and thioesters.[1,10] These additives react with peroxides to form more stable alcohols. Often, both primary and secondary antioxidants are used together to protect polypropylene from oxidation.

Formaldehyde-Protein Crosslinking

Chemical fixation of tissues is a common technique used in histology for purposes of preservation and hardening.[12,13] While a number of different chemical fixatives are used in histology, formaldehyde is one of the most common.[12] Formalin (a formaldehyde/water mixture) was first used to harden tissues in 1893 and has been a widely accepted chemical fixative since.[14] Formaldehyde works as a fixative by chemically cross-linking proteins, forming a large network polymer. The cross-linking chemical reaction in tissue between formaldehyde

[11] Gensler, R., Plummer, C. J.G., Kausch, H.-H., Kramer, E., et al. "Thermo-Oxidative Degradation of Isotactic Polypropylene at High Temperatures: Phenolic Antioxidants versus HAS." *Polym. Degrad. Stab.*, (2000) 67(2):195–208.

[12] Hewitson, T. D., Wigg, B., Becker, G. J. "Tissue Preparation for Histochemistry: Fixation, Embedding, and Antigen Retrieval for Light Microscopy." *Histology Protocols*. Ed. Tim D. Hewitson and Ian A. Darby. Vol. 611. Totowa, NJ: Humana Press, 2010.

[13] Thavarajah, R., Mudimbaimannar, V., Rao, U., Ranganathan, K., et al. "Chemical and Physical Basics of Routine Formaldehyde Fixation." *J. Oral Maxillofac. Pathol.*, (2012) 16(3):400–405.

[14] Puchtler, H., Meloan, S. N. "On the Chemistry of Formaldehyde Fixation and Its Effects on Immunohistochemical Reactions." *Histochemistry*, (1985) 82(3):201–204.

and proteins is outlined in Figure 4.[13] Formaldehyde can react with amino acid chains in proteins to form methylene bridges between polypeptide chains.[12,13,14]

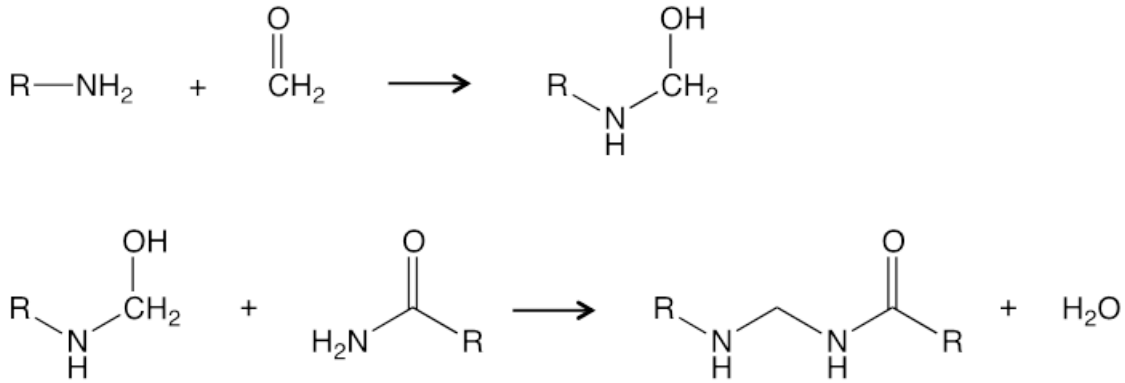

Figure 4. Simplified reaction schematic of proteins with formalin.

The resulting polymer has a much higher stiffness due to the newly formed chemical cross-links. This increase in stiffness allows tissue samples to be sectioned by various techniques including microtoming.

PROLENE

Ethicon's antioxidant stabilized polypropylene-based resin is known by the tradename PROLENE. The resin was determined to be "safe and effective for use" in nonabsorbable surgical sutures by the FDA in 1969,[15] and has been used ever since. PROLENE sutures are manufactured by a melt spinning process (previously described in this report).[16] In addition to manufacturing PROLENE sutures, Ethicon has knitted PROLENE filaments in to mesh materials used in hernia repair, and in the treatment of pelvic organ prolapse and stress urinary incontinence.

Composition

As with many commercially available resin compounds, Ethicon's PROLENE resin is comprised of several raw material ingredients in addition to the base isotactic polypropylene. The additional formulation ingredients and corresponding loading level ranges are:[17]

- Calcium Stearate – 0.25–0.35% −a lubricant to help reduce tissue drag and promote tissue passage
- Santonox R – 0.10–0.30% – a primary hindered phenol antioxidant
- Dilauralthiodipropionate (DLTDP) – 0.40-0.60% −a secondary thioester antioxidant
- Procol LA-10 – 0.25–0.35% – a lubricant to help reduce tissue drag and promote tissue passage
- Copper Phthalocyanate (CPC) Pigment – 0.55% max. – a colorant to enhance visibility (in blue filaments only)

[15] NDA – 4.16.1969 PROLENE FDA Approval (ETH.MESH.09625731–09625737).

[16] FDA – Reclassification.pdf (ETH.MESH.10665538–10665565).

[17] John Karl's January 23, 2003 Memo titled PROLENE Resin Manufacturing Specifications (Eth.Mesh.02268619–02268621).

A summary of the full resin history including information on compounding, manufacturing, and formulation changes can be found in Karl's memo entitled "PROLENE Resin Manufacturing Specifications."[17]

PROLENE Biocompatibility

The U.S. Food and Drug Administration (FDA) stipulates that a medical device "should not, either directly or through the release of their material constituents: (i) produce adverse local or systemic effects; (ii) be carcinogenic; or, (iii) produce adverse reproductive and developmental effects."[18] The device manufacturer must follow FDA guidelines and evaluate material biocompatibility with certain tests that can vary depending on factors such as the intended application (e.g., duration and location of patient contact); alternatively, a manufacturer may not need to conduct all biocompatibility tests if its device is composed of materials that have been well characterized physically and chemically and have a long history of safe use.[18] The protocols for these tests are contained in standards established by the U.S. Pharmacopeia (USP), the International Organization for Standardization (ISO), and ASTM International.[19]

Prior to the FDA's approval of PROLENE sutures in 1969,[15] Ethicon performed multiple animal implant studies to determine PROLENE's effect *in vivo*. These studies, performed on rats, dogs, and rabbits,[20] primarily investigated the tissue reactions caused by both colored and colorless sutures implanted in animal hosts. It was found that, the "polypropylene suture was well tolerated by tissue, evoked a reaction of the type associated with relatively non-irritation (sic) foreign bodies, was not absorbed during the test periods, did not lose appreciable tensile strength, and was not carcinogenic."

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[18] FDA Guidelines on Premarket Approval of Medical Devices, accessed July 25, 2015, available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050490.htm#bio.

[19] FDA Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, accessed July 25, 2015, available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073790.htm.

[20] PROLENE suture NDA Preclinical Studies.pdf (ETH.MESH.09626242–09626359).

As mentioned previously, in 1969 the FDA approved PROLENE sutures as a "new drug," stating that "We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling."[15] Later, in 1990 the Center for Devices and Radiological Health (CDRH) of the FDA reclassified nonabsorbable polypropylene surgical sutures from class III to class II[16] stating that "it is apparent to the FDA that a class III designation for nonabsorbable polypropylene surgical suture constitutes overregulation." The FDA class II designation is used for devices for which general controls are insufficient to "assure a device's safety and effectiveness" but "sufficient information exists to establish a performance standard to provide such an assurance."[16] The FDA concluded that the development of the performance standard for class II devices was of low priority.[16]

In addition to conducting animal studies to analyze PROLENE sutures, Ethicon also performed studies in rabbits[21] and rats[22] to analyze the tissue reaction to implanted meshes comprised of knitted PROLENE filaments. These studies showed that "[t]he tissue reaction to TVT mesh was characterized by generally mild chronic inflammation during the 28-day [rat] study, which was comparable to the tissue reaction observed for PROLENE polypropylene mesh" and that "[t]he reactions to PROLENE mesh were similar in type and extent to the response elicited by Marlex mesh implanted as a control" in the rabbit study, further supporting PROLENE's biocompatibility.

In order for PROLENE mesh to be used as a permanent tissue implant, Ethicon must comply with ISO 10993[23] and analyze the cytotoxicity, sensitization, and genotoxicity, among other tests, of the PROLENE mesh.[24] The safety of PROLENE meshes has been demonstrated through a long history of clinical use of PROLENE sutures as well as confirmatory cytotoxicity

[21] 1973 Rabbit Study for PROLENE Mesh.pdf (ETH.MESH.10575607 – 10575613).

[22] PSE 97-0197.pdf (ETH.MESH.05315240 – 05315295).

[23] ISO 10993-1-2009.pdf.

[24] Eth Mesh 04384112 – Biocompatibility Risk Assessment for the TVT-L Device – June 6 2001.pdf (ETH.MESH.04384112 – 04284125).

tests. Because of the historical clinical safety of PROLENE sutures, no additional in-depth testing was considered necessary as all of the relevant biological effects listed in ISO 10993 had been previously investigated.[23]

Mesh as a Medical Device

Introduction to Surgical Mesh

Surgical meshes are typically implanted in the body for the repair of soft tissues, including abdominal wall defects (hernias), uro-gynecological applications, and cardio-thoracic defects.[25]

The design and composition of surgical mesh has evolved significantly over time. The first examples were introduced in the early 20th century, and were composed of metals like silver, tantalum, and stainless steel. All were discontinued due to complications, including corrosion, metal fragmentation, erosion, and infection.[25] Polymeric mesh materials date back to the 1930s, when polypropylene mesh was first used to treat abdominal hernias.[27]

Due to its decades-long success in the field of hernia management, surgical mesh has also become prevalent in the treatment of urological and gynecological conditions, such as urinary incontinence and pelvic organ prolapse. The underlying principle behind these interventions is simple: mesh structures comprised of biocompatible materials are used to reinforce existing tissue, providing both anatomic and functional results.[26]

Current Surgical Mesh Materials

The pelvic organs, which include the bladder, urethra, uterus, vagina, perineal body, and rectum, are maintained in position via the pelvis and a network of muscles and connective tissues. Pelvic organ prolapse is a condition characterized by the downward displacement of some or all pelvic

[25] Pandit, A. S., Henry, J. A. "Design of Surgical Meshes – an Engineering Perspective." *Technol. Health Care*, (2004) 12(1):51–65.

[26] Dällenbach, P. "To Mesh or Not to Mesh: A Review of Pelvic Organ Reconstructive Surgery." *Int. J. Womens Health*, (2015):331.

organs, sometimes resulting in a bulge within the vagina. Lack of support for the urethra can also lead to stress urinary incontinence.[27]

The use of surgical mesh for female pelvic surgery dates back to the 1930s and 1950s, when nylon (polyamide) and Mersilene® (polyethylene terephthalate) were investigated as potential biomaterials for urinary incontinence surgery, respectively.[27,28,29] Today, surgical mesh used in pelvic organ prolapse repair, and in the treatment of stress urinary incontinence is predominantly manufactured from monofilament polypropylene in various weights and pore sizes.[30] The first FDA-approved synthetic mesh manufactured specifically to treat urinary incontinence was produced by Island Biosurgical, Inc., which was demonstrated to be substantially equivalent to Marlex® polypropylene, in 1996.[26,31] That same year, Ethicon obtained approval to market modified PROLENE, a mesh constructed of knitted filaments of an extruded polypropylene based material, for repair of "hernia and other fascial deficiencies."[32]

One of the earliest FDA-approved polypropylene-based products for female pelvic reconstructive surgery was Gynemesh® (Ethicon).[26,33] Since then, several medical device manufacturers have obtained approval to market polypropylene meshes for similar use, including C.R. Bard,[34] American Medical Systems,[35] Mpathy Medical Devices,[36] Sofradim,[37]

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[27] Kanagarajah, P., Ayyathurai, R., Gomez, C. "Evaluation of Current Synthetic Mesh Materials in Pelvic Organ Prolapse Repair." *Curr. Urol. Rep.*, (2012) 13(3):240–246.

[28] Birch, C. "The Use of Prosthetics in Pelvic Reconstructive Surgery." *Best Pract. Res. Clin. Obstet. Gynaecol.*, (2005) 19(6):979–991.

[29] DeBord, J. R. "Prostheses in Hernia Surgery: A Century of Evolution." *Abdominal Wall Hernias*. Ed. Robert Bendavid, Jack Abrahamson, Maurice E. Arregui, Jean Bernard Flament, et al. New York, NY: Springer New York, 2001.

[30] Edwards, S. L., Werkmeister, J. A., Rosamilia, A., Ramshaw, J. A. M., et al. "Characterisation of Clinical and Newly Fabricated Meshes for Pelvic Organ Prolapse Repair." *J. Mech. Behav. Biomed. Mater.*, (2013) 2353–61.

[31] Island Biosurgical, Inc. Island Biosurgical Bolster. 510(k) #K960101.

[32] Ethicon, Inc. Modified PROLENE Polypropylene Mesh Nonabsorbable Synthetic Surgical Mesh. 510(k) #962530.

[33] Ethicon, Inc. Gynemesh PROLENE Soft (Polypropylene) Mesh. 510(k) # K013718.

[34] C.R. Bard, Inc. Avaulta™ Solo Support System and Avaulta™ Plus Biosynthetic Support System. 510(k) #K063712.

[35] American Medical Systems. AMS Large Pore Polypropylene mesh. 510(k) #K033636.

and Coloplast.[38] Mesh products are also marketed as kits that include not only a precut mesh, but also tools to aid its implantation. Manufacturers of polypropylene-based mesh kits include C.R. Bard,[39] American Medical Systems,[40] Mentor,[41] MLE, [42] and Boston Scientific.[43,44]

Suture and Mesh Literature Review

As part of its analysis, Exponent has considered peer-reviewed literature that investigated the use of polypropylene sutures and mesh as medical implants. Our account and summary points of these literature papers are given below.

Clavé

Clavé *et al.*[45] studied 100 explanted mesh samples that were removed due to complications. After explantation, samples were rinsed and placed in a 4% neutral buffer formalin solution. After storage in the formalin solution, samples for Fourier transform infrared spectroscopy (FTIR) were washed in a sodium hypochlorite (NaOCl) solution for 26 hours, washed with deionized water, and then extracted with pure cyclohexane for 24 hours at room temp. Clavé did not verify that the cleaning protocol entirely removed biological material from the mesh, stating that, "FTIR absorption bands between 1,615 and 1,650 cm^{-1} could be attributed either to carboxylate carbonyl or to residual products of biological origin." Clavé further stated, "FTIR analysis neither confirmed nor excluded oxidation of PP in the *in vivo* environment."

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[36] Mpathy Medical Devices, Ltd. Minimesh® polypropylene mesh. 510(k) #K041632.

[37] Sofradim Production. Parietene™ Duo Polypropylene mesh and Parietene™ Quadra Polypropylene mesh. 510(k) #K072951.

[38] Coloplast A/S. Restorelle™ polypropylene mesh. 510(k) #K103568.

[39] C.R. Bard, Inc. Bard® InnerLace™ BioUrethral Support System. 510(k) #K031295.

[40] American Medical Systems. BioArc TO™ Subfascial Hammock. 510(k) #K040538.

[41] MentorCorp. Mentor ObTape™ Trans-obdurator Surgical Kit. 510(k) #042851.

[42] MLE, Inc. Suture Fixation Device. 510(k) #K021834.

[43] Boston Scientific Corp. Pinnacle Pelvic Floor Repair Kit II. 510(k) #081048.

[44] Boston Scientific Corp. Pinnacle Lite Pelvic Floor Repair Kit. 510(k) #122459.

[45] Clavé, A., Yahi, H., Hammou, J.-C., Montanari, S., et al. "Polypropylene as a Reinforcement in Pelvic Surgery Is Not Inert: Comparative Analysis of 100 Explants." *Int. Urogynecology J.*, (2010) 21(3):261–270.

While the use of FTIR can be very beneficial in the field of polymer science, it is important to understand the limitations. One such limitation is the precision of the sampling volume. The penetration depth of the infrared (IR) beam into the sample is typically 0.5 µm to 5 µm, depending on experimental conditions such as the wavelength of light and the angle of incidence.[46] According to Ethicon documents, the depth of microcracks in explanted PROLENE sutures has been measured to be 0.5–4.5 µm.[47] Furthermore, the spot size for sampling may range from several millimeters down to 15 µm, depending on microscope attachment.[48] Therefore, a given FTIR spectrum may consist of functional groups from neighboring materials and the underlying bulk fiber material.

Clavé also analyzed both pristine exemplar mesh and explanted polypropylene mesh materials by differential scanning calorimetry (DSC). DSC is an analysis technique used to evaluate the thermal properties of materials such as glass transition temperature, melting point and heat of fusion. His study concluded that, "no difference between DSC thermograms of pristine and degraded samples was found."

Clavé's only claimed evidence of "degradation" is the presence of a cracked outer layer on the explants, which was imaged via scanning electron microscopy (SEM). However, Clavé failed to fully remove the biological material from these samples as evidenced by the intact tissue present in the SEM images and neglected to analyze or to chemically identify the observed cracked layer. Unlike the samples that underwent FTIR that were cleaned with NaOCl, the samples that were analyzed by SEM did not undergo any cleaning prior to imaging. Instead, the samples were fixed in formalin, and then further fixed and preserved with 1% glutaradehyde and post fixed with a 1% osmium tetroxide solution. Finally, these samples were dehydrated with a series of ethanol solutions and dried using hexamethyldisilazane before being coated with gold-palladium. In short, Clavé presumes the cracked outer layer to be evidence of "degradation,"

[46] ATR – Theory and Applications.pdf Pike Technologies.

[47] "Crack Depth in Explanted PROLENE Polypropylene Sutures memo (ETH.MESH.12831405 – 12831406).

[48] EAG FTIR Technique Note.

without generating any data that identified the chemical composition of the outermost layer. Clavé also did not conclusively determine whether there was any evidence of polypropylene degradation, including oxidation.

de Tayrac

A separate paper by de Tayrac *et al*. investigated Clavé's conclusion regarding a correlation between infection and polypropylene "degradation." In this study, de Tayrac *et al.* implanted polypropylene mesh materials (unspecified manufacturer) into Wistar rats along with *E. coli* bacteria for 30 days.[49] After the mesh was harvested, it was not formalin fixed, but rather it was washed in a solvent, dimethyl sulfoxide (DMSO), and ultrasonically shocked. SEM images of these samples prior to ultrasonic shock treatment showed evidence of transverse cracking, but after the ultrasonic treatment the mesh filaments appeared smooth with no persisting microscopic evidence of a cracked outer layer. Unlike Clavé *et al.*, de Tayrac concluded that the originally observed transverse cracking "appeared to concern only the biofilm, with no effect on the implant thread itself."

Costello

To evaluate the physiochemical changes that are indicative of oxidation allegedly associated with polypropylene *in vivo*, Costello *et al.* analyzed fourteen explanted polypropylene/expanded polytetrafluoroethylene (PTFE) composite hernia meshes.[50] These composite hernia meshes were not manufactured by Ethicon, none were comprised of PROLENE, and had different knit structures and pore sizes, i.e., the multi-polymer meshes analyzed were inherently different from Ethicon's PROLENE mesh and therefore the conclusions reached in this study are not directly applicable to PROLENE mesh material or design.

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[49] De Tayrac, R., Letouzey, V. "Basic Science and Clinical Aspects of Mesh Infection in Pelvic Floor Reconstructive Surgery." *Int. Urogynecology J.*, (2011) 22(7):775–780.

[50] Costello, C. R., Bachman, S. L., Ramshaw, B. J., Grant, S. A. "Materials Characterization of Explanted Polypropylene Hernia Meshes." *J. Biomed. Mater. Res. B Appl. Biomater.*, (2007) 83B(1):44–49.

In this study, Costello preserved and stored the explanted meshes in a 10% v/v formalin solution before the tissue surrounding the mesh was removed in a NaOCl bath at 37 ˚C for 2 hours. Costello did not perform any chemical analysis to verify the extent to which the cleaning procedure removed bulk tissue and other biological residues from the mesh surface.

Through SEM examination, Costello observed "cracks, fissures, and increased surface roughness," as well as peeling on the surface of the explanted samples, which can be explained by the presence of buildup of foreign material on the exterior of the mesh filaments. Costello failed to perform any type of chemical characterization on this outer "peeling" material and, therefore, the chemical composition of this layer was simply undetermined in the study. Using differential scanning calorimetry (DSC) techniques, Costello claimed that a decrease in melting point was observed in the explanted samples when compared to the exemplar mesh material. Melt temperature suppression could be explained in many ways. For example, the mesh material has the potential to undergo plasticization *in vivo* as seen in a study performed by Ethicon on PROLENE sutures explanted from dogs.[51] This study found that after seven years *in vivo,* PROLENE sutures showed an increase in elongation at break and a decrease in modulus, which are consistent with plasticization.

Through a compliance test measuring the work required to "bend the mesh in half and push it through a 2.92 cm^2 slot," Costello claimed to demonstrate a decrease in compliance of the explanted mesh. Costello alleged that this decrease in compliance "is evidence of oxidation,"[50] but failed to take into account the "permanent deformation of the material while *in vivo,*"[50] which is a result of the natural stress relaxation of the polymer. The folded geometry will artificially alter the apparent compliance (stiffness/rigidity) of the mesh. The flexural rigidity of a material is directly proportional to the modulus of elasticity and the moment of inertia, which is a geometrical term based on specimen geometry.[52] The "permanent deformation" of the explanted mesh makes a direct comparison of the rigidity of the exemplar and explants more

[51] Ethicon's Seven Year Dog Study.

[52] Lubliner, J., Papadopoulos, P. *Introduction to Solid Mechanics: An Integrated Approach*. New York, NY: Springer, 2014.

complicated due to different moments of inertia. To truly compare the explanted and exemplar mesh materials, it is necessary to calculate the modulus of elasticity, which is independent of specimen geometry. Costello also reported that the total work required to bend the mesh and push it through the slot was greater for explanted mesh materials than for an exemplar mesh This is another example of Costello's lack of fundamental understanding of the importance of specimen geometry in mechanical testing. The work required to bend a sample is related to its stiffness, which as discussed above, is a function of both the material's modulus *and* specimen geometry. Thus the increase in total work observed in this test is most likely due to the folded specimen geometry, not oxidation or degradation. Furthermore, Costello's claim of a decrease in compliance (increase in stiffness/rigidity) is contrary to the results of the Seven Year Dog study performed by Ethicon's scientists.[51] This study found that after seven years *in vivo*, PROLENE sutures decreased in stiffness (increase in compliance) as evidenced by a reduction in modulus of PROLENE sutures after seven years *in vivo*.

Costello also "most likely" attributed the broadening of the melting point observed in the explanted samples to *in vivo* oxidation. Their rationale is that oxidized polypropylene will result in an increase in polydispersity, which would correlate to a broader observed melting point. However, the degree to which this broadening occurred was not reported, and as such is difficult to analyze. Melting point broadening could also be due to variability in the concentration of low molecular weight species that may have been absorbed by the material while *in vivo*. Additionally, unexplained endothermic and exothermic peaks are seen in the DSC data at 230°C in the exemplar curve (Composix E/X), 275°C, 320°C and 340°C in the Subject #2 curve, and 335°C in the Subject #9 curve, which are on the order of the melting point transition, thus rendering any perceived small change in the broadening of the melting point unfounded.

Finally, Costello stated that "[o]xidized materials are expected to undergo some degree of weight loss as the material is degraded by the body. Thus oxidized materials should have less weight available to be lost during TGA." This statement shows a fundamental misunderstanding of TGA analysis. Typically, TGA data are used to report the onset of degradation or the residual

(often inorganic) mass at the end of the test. Data is reported as a *percentage* of the original weight of the sample placed in the sample chamber. Assuming homogeneous mixing of any inorganic compounds within a polymer sample, the degree of weight loss determined by TGA will be the same regardless of whether or not the polymer has experienced oxidation. In the absence of any inorganic filler, 100% weight loss of the sample is expected if the TGA analysis is carried through to completion. Furthermore, Costello's data showed a shift to higher temperatures in the peak of the derivative of the mass loss with temperature curve for explanted samples (Subject #2 and Subject #9). This demonstrates the exemplar mesh degraded at a higher rate at lower temperatures than the explanted mesh materials, which challenges, if not contradicts, Costello's hypothesis of oxidation.

Cozad

To understand tissue-material interactions occurring *in vivo*, Cozad *et al.* examined eleven explanted composite hernia meshes (not PROLENE, and not manufactured by Ethicon) that contained polypropylene and expanded polytetrafluoroethylene (ePTFE) components.[53] These composite meshes, analysis, authors, and methodology were very similar to the work previously outlined by Costello,[50] and will not be repeated again here in complete detail. Cozad, like Costello, performed analysis (FTIR, DSC, TGA and SEM imaging) on explanted mesh materials without verifying that the samples were fully cleaned. In fact, the researchers readily admitted choosing sections to analyze which were "the most 'pristine-like' sites with no apparent tissue adsorption," strongly suggesting that they were aware that the overall samples were not adequately cleaned. Furthermore, Cozad attributed an increase in FTIR absorbance peaks at 2850 cm^{-1} to "surface hydrocarbon formation," again suggesting that the explanted mesh was not fully cleaned before analysis was performed. But instead of developing a more thorough cleaning procedure, Cozad *et al.* simply continued with their analysis without any apparent concern for the possibility of inaccurate results and without considering that the

[53] Cozad, M. J., Grant, D. A., Bachman, S. L., Grant, D. N., et al. "Materials Characterization of Explanted Polypropylene, Polyethylene Terephthalate, and Expanded Polytetrafluoroethylene Composites: Spectral and Thermal Analysis." *J. Biomed. Mater. Res. B Appl. Biomater.*, (2010) 455–462.

observed crust may be biologic in nature. The authors stated that the polypropylene portions of the mesh oxidized, while the ePTFE portions cross-linked *in vivo*. One of the major sources for this conclusion is the FTIR data that showed a nearly identical peak seen at 1730 cm^{-1} in both the explanted polypropylene and the ePTFE. It is unlikely that crosslinking in ePTFE and oxidation in polypropylene would show nearly identical peaks (i.e. the peaks are extremely similar in shape and location). Further, the authors give no plausible reason the ePTFE could crosslink *in vivo* as most studies, some of which are referenced in the Cozad article, require irradiation or high temperature and vacuum to crosslink PTFE.[54,55,56] Rather, a more likely scenario is that the 1730 cm^{-1} peak observed is actually an artifact or residue of sample handling, such as adhesive used in electron microscopy. Adhesive acrylate peaks look strikingly similar to the 1730 cm^{-1} peaks reported by Cozad *et al*.

Liebert

Liebert *et al.*[57] implanted polypropylene sutures with and without antioxidants (neither of which were PROLENE) into the backs of hamsters. They described evidence of oxidation in the sutures without antioxidants, but claimed to see no evidence of oxidation in sutures with antioxidants after 108 days of implantation. Liebert tracked degradation by monitoring carbonyl content via FTIR, molecular weight by gel permeation chromatography (GPC) and tan δ by dynamic mechanical analysis (DMA), and found no change in the filaments with antioxidants. They concluded that the oxidation process "is retarded effectively by using an antioxidant." This finding is in concert with the historical use of antioxidant stabilizers in polypropylene formulations for implantable materials.

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[54] Lappan, U., Geißler, U., Lunkwitz, K. "Changes in the Chemical Structure of Polytetrafluoroethylene Induced by Electron Beam Irradiation in the Molten State." *Radiat. Phys. Chem.*, (2000) 59(3):317–322.

[55] Pugmire, D. L., Wetteland, C. J., Duncan, W. S., Lakis, R. E., et al. "Cross-Linking of Polytetrafluoroethylene during Room-Temperature Irradiation." *Polym. Degrad. Stab.*, (2009) 94(9):1533–1541.

[56] Lappan, U., Geißler, U., Häußler, L., Jehnichen, D., et al. "Radiation-Induced Branching and Crosslinking of Poly(tetrafluoroethylene) (PTFE)." *Nucl. Instrum. Methods Phys. Res. Sect. B Beam Interact. Mater. At.*, (2001) 185(1-4):178–183.

[57] Liebert, T. C., Chartoff, R. P., Cosgrove, S. L., McCuskey, R. S. "Subcutaneous Implants of Polypropylene Filaments." *J. Biomed. Mater. Res.*, (1976) 10(6):939–951.

Mary

Comparison of PVDF (Teflene, Péters Laboratoire Pharmaceutique) and polypropylene (PROLENE, Ethicon) sutures implanted in female dogs for periods of time ranging from 4 hours to 2 years were studied by Mary *et al*.[58] Explanted samples examined via SEM and FTIR were cleaned with an enzyme incubation technique, rinsed in buffer and deionized water solutions and dried. Comparative FTIR spectra for PVDF and polypropylene enzymatically cleaned explants were tracked with time, only presenting the absorbance data at 1740 cm^{-1}, the peak assigned to carbonyl stretching. In all samples tested, Mary reported a rapid increase in carbonyl presence to a maximum value, followed by a decrease and then stabilization. This decrease in carbonyl intensity, which occurred at different times for each sample, showed absolutely no support for Mary's theory of polypropylene *in vivo* degradation. There is no scientific basis for a claim of partial recovery of degradation, as indicated by the reduction in carbonyl intensity. Instead, this data suggests that Mary sampled a material other than the surface of the polypropylene filament, such as biologic material which changed with implantation time. The lack of testing to verify complete sample cleaning further supports this hypothesis. Alternatively, Mary may have sampled locations where there was natural variation in the concentration of any carbonyl-containing molecules within the polymer matrix. Furthermore, microscopic examination of cleaned polypropylene samples showed an absence of cracking in both sample types at 6 months, the time at which the carbonyl signal in the FTIR had already begun to stabilize, suggesting a lack of correlation between reported carbonyl functionality and observed cracking.

Wood

In order to control for the effects of physiological variability among different patients, Wood *et al.* studied three explanted mesh samples from the same patient. The three different mesh samples were comprised of polypropylene, expanded polytetrafluoroethylene (ePTFE), and

[58] Mary, C., Marois, Y., King, M. W., Laroche, G., et al. "Comparison of the In Vivo Behavior of Polyvinylidene Fluoride and Polypropylene Sutures Used in Vascular Surgery:" *ASAIO J.*, (1998) 44(3):199–206.

polyethylene terephthalate (PET), and were implanted to treat three separate ventral hernias.[59] The patient has a medical history of gout, morbid obesity, tobacco usage, and sleep apnea. The authors did not state why there were different materials implanted in the same patient.

After explantation, all specimens were placed in a formalin solution followed by immersion in a NaOCl solution to remove residual tissue. After the cleaning procedure, Wood collected FTIR spectra of each of the explants and corresponding exemplar mesh materials to identify chemical changes on the surface of the mesh. FTIR revealed an increase in carbonyl functionality on each of the explanted specimens when compared to pristine exemplar meshes, "which could indicate the presence of scar tissue and/or chemical degradation." The presence of scar tissue on the cleaned specimens is further supported by photographs of the cleaned and explanted mesh which clearly show evidence of attached tissue and discoloration associated with incomplete cleaning. Additionally, the FTIR spectra of explanted ePTFE and PET show an unexplained increase of absorption bands at 3100–2800 cm^{-1}, which have been attributed to C-H bond stretching.[60] This increase is unexpected[61,62] in the degradation of both polypropylene and ePTFE, which further indicates Wood's lack of sufficient cleaning. Wood goes on to evaluate the cleaned mesh materials using SEM microscopy and modulated differential scanning calorimetry, but does not provide evidence of further or complete cleaning. These results cannot be relied upon to provide conclusive evidence of degradation due to the presence of tissue and/or other contaminants.

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[59] Wood, A. J., Cozad, M. J., Grant, D. A., Ostdiek, A. M., et al. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." *J. Mater. Sci. Mater. Med.*, (2013) 24(4):1113–1122.

[60] Chen, Z., Hay, J. N., Jenkins, M. J. "FTIR Spectroscopic Analysis of Poly(ethylene Terephthalate) on Crystallization." *Eur. Polym. J.*, (2012) 48(9):1586–1610.

[61] Fotopoulou, K. N., Karapanagioti, H. K. "Surface Properties of Beached Plastics." *Environ. Sci. Pollut. Res.*, (2015) 22(14):11022–11032.

[62] Atta, A., Fawzy, Y. H. A., Bek, A., Abdel-Hamid, H. M., et al. "Modulation of Structure, Morphology and Wettability of Polytetrafluoroethylene Surface by Low Energy Ion Beam Irradiation." *Nucl. Instrum. Methods Phys. Res. Sect. B Beam Interact. Mater. At.*, (2013):30046–53.

Guelcher

Guelcher *et al.* studied the *in vitro* oxidation of both polypropylene pellets without antioxidants and polypropylene mesh with antioxidants.[63] The samples were placed in a 20 wt% hydrogen peroxide (H_2O_2) solution containing 0.1 M $CoCl_2$ for up to five weeks. A similar solution was used previously by Zhao *et al.* as one component of a regimen designed to mimic "the respiratory burst of adherent macrophages and foreign-body giant cells" on a poly(etherurethane) (PEU) elastomer.[64] Zhao *et al.* hypothesized that "biological components in the body fluids, oxidative agents, and stress or strain act synergistically to produce the stress cracking of polyurethanes."[64] To mimic the stress cracking morphology of PEU *in vivo* from a rat model after 5 – 10 weeks of implantation, Zhao *et al.* designed an *in vitro* treatment that incorporated these three components. Specifically, the PEU specimens were first pretreated and prestressed by soaking the PEU in acetone to extract additives and by stretching to 400 % elongation. Secondly, the PEU samples were incubated with a biological fluid, such as blood plasma, at 37 ˚C for 7 days. Finally, the samples were treated with an oxidizing solution, composed of 10 % hydrogen peroxide and 0.1 M $CoCl_2$, at 50 ˚C for 9 – 10 days. To validate this regimen, Zhao *et al.* examined the surface morphology and utilized several chemical characterization techniques to inspect the treated PEU specimens comparing the explants and controls, which included biological fluid only or oxidizing solution only treatments. Although the oxidizing solution alone resulted in some PEU oxidation as determined by FTIR and GPC, the surface morphology of the polymer was vastly different from that of a PEU explant. To achieve a PEU surface morphology similar to that of an explant, proteins from the blood plasma were required, supporting the hypothesis that plasma proteins synergistically enhanced PEU oxidation.

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[63] Guelcher, S. A., Dunn, R. F. "Oxidative Degradation of Polypropylene Pelvic Mesh in Vitro." *Int Urogynecol J*, (2015) 26(Suppl 1):S55–S56.

[64] Zhao, Q. H., McNally, A. K., Rubin, K. R., Renier, M., et al. "Human Plasma Macroglobulin Promotesin Vitro Oxidative Stress Cracking of Pellethane 2363-80A:In Vivo Andin Vitro Correlations." *J. Biomed. Mater. Res.*, (1993) 27(3):379–388.

The goal of Zhao's accelerated oxidation experiment was to develop an *in vitro* oxidation protocol that would result in a similar morphology and chemical properties when compared to *in vivo* explants for a specific polymer, PEU, but only at a single time point. For example, he compared *in vitro* samples exposed to 7 days of biological fluids plus 10 days of an oxidative environment to samples that were exposed to 35 days of an *in vivo* environment and concluded the *in vitro*, accelerated conditions are representative of the *in vivo* environment. Though this may be valid for the single time point compared, the study does not consider rate effects and it is likely at other time points the comparison between *in vitro* and *in vivo* samples will be different. The Zhao study makes no claims to address this, but a more robust method would include additional data points at extended exposure times to demonstrate the rate of change or acceleration factor is similar between the *in vitro* and *in vivo* environments. Additionally, the Zhao study relies on SEM and chemical analysis (FTIR and GPC) to compare the *in vitro* and *in vivo* samples. Mechanical and physical testing that quantifies these characteristics would provide a more complete understanding of any changes in the material upon exposure to the representative conditions.

Dr. Guelcher provided an explanation of polypropylene oxidation similar to that of PEU oxidation hypothesized by Zhao; that is, "we reasoned that the combination of mechanical stress, the secretion of reactive oxygen species (ROS) by adherent inflammatory cells associated with the foreign body reaction, and the susceptibility of polypropylene to oxidation leads to environmental stress cracking as a potential root cause of failure of polypropylene pelvic mesh in patients."[63] However, Dr. Guelcher did not include a biological fluid or mechanical stress in his experimental protocol, and additionally used a different concentration of H_2O_2 (20 % vs. 10 % in Zhao *et al.*). Most importantly, Dr. Guelcher did not consider comparing the morphology of polypropylene explants with polypropylene subjected to his oxidizing protocol. Instead, Dr. Guelcher simply applied a portion of Zhao *et al.*'s oxidizing protocol for a different polymer, without validating the appropriateness of the method for polypropylene or characterizing the oxidation rate in relation to the actual *in vivo* environment. In fact, as can be seen from Guelcher's one and only SEM image of polypropylene mesh after treatment in the $H_2O_2/CoCl_2$

solution for five weeks, the "pitting and flaking" observed in the samples is completely inconsistent with the morphology of explanted polypropylene mesh samples, thus calling into question the validity of his method used for polypropylene and demonstrating that Zhao's results for PEU cannot be extrapolated to polypropylene. In addition, Dr. Guelcher also did not perform GPC, let alone any mechanical or physical testing, to confirm oxidative degradation. As previously mentioned, chemical analysis by FTIR alone was insufficient to determine polypropylene degradation.

Hafeman *et al.*[65] used the same oxidative medium (20 % H_2O_2 with 0.1 M $CoCl_2$) as Dr. Guelcher to evaluate *in vitro* degradation of poly(esterurethane) (PEUR) based on two different isocyanates. Specifically, PEUR scaffolds were prepared from lysine triisocyanate (LTI) or a trimer of hexamethylene diisocyanate (HDIt). Additionally, LTI-based PEUR was synthesized from a 6C polyester triol (6C/LTI) or from a 7C triol (7C/LTI). Although the *in vitro* degradation rate of the LTI-based PEUR scaffolds more closely approximated that of the *in vivo* degradation of the same PEUR in a rat model, the *in vitro* degradation rate of HDIt-based PEUR scaffolds was substantially different than the *in vivo* degradation. In the same study, the amounts of degradation products from 6C/LTI and 7C/LTI scaffolds incubated in PBS were also significantly different throughout the 36-week duration, further highlighting the material dependence on degradation rate. In addition, the H_2O_2 and NO production by RAW 264.7 cells (a macrophage cell line) cultured *in vitro* on 6C/LTI scaffolds was significantly different in comparison to cells cultured with 6C/HDIt scaffolds, confirming that the oxidative environment created by adherent inflammatory cells in response to a material is highly dependent on the composition of the polymer. The results from the Hafeman study strongly emphasized the material dependence of degradation rate *even for the same class of polymers*, underlining the inappropriateness of extrapolating a single *in vitro* environment that simulates the *in vivo* environment for one material to other materials. Dr. Guelcher clearly did not consider these

[65] Hafeman, A.E., Guelcher, S.A., et al. "Characterization of the degradation mechanisms of lysine-derived aliphatic poly(ester urethane) scaffolds." *Biomaterials* (2011) 32:419-429.

factors when utilizing a portion of Zhao's oxidative medium, which was designed for PEU, to evaluate *in vitro* degradation of polypropylene mesh.

Talley

Talley *et al.* recently examined the potential of three commercial mid-urethral slings, including Gynecare TVT mesh,[66] to oxidize when subjected to the same *in vitro* oxidative condition as described previously by Guelcher.[63] In their investigation, the mesh was incubated for 5 weeks in an oxidative medium while periodically monitoring the surface chemistry and appearance by FTIR and SEM. The authors used FTIR to identify the presence of carbonyls and hydroxyl functional groups, which they claim are the two major chemical species formed as a result of polypropylene chemical oxidation (the authors further claim hydroxyls can be used to identify the formation of a hydroperoxide intermediate). The authors rely on statistical analysis to identify peaks due to these functional groups by integrating the spectra over defined wavenumber ranges. However, the authors' methods for data analysis, interpretation and reporting are scientifically flawed rendering their findings unreliable.

First, select peaks in the FTIR data which the authors ascribe as evidence of oxidation are most likely from residual water in their sample and not surface oxidation of polypropylene mesh. Figure 5 is an overlay of the LYNX mesh (manufactured by Boston Scientific) FTIR data after five weeks of exposure to the oxidative medium from Talley's publication (black line) and deionized water (red line). The two blue arrows highlight the two peaks claimed by Talley to be signs of polypropylene oxidation. Water has two vibrational absorption bands that are nearly identical in peak position and shape to the peaks flagged by Talley. The peak at ~3400 cm^{-1} could equally arise from hydroxyl vibrational stretches shared in water and the peak centered at ~1650 cm^{-1} can be attributed to a bending mode of the molecule. Not only do the shape and positions of the water peaks match Talley's data, but the relative ratios of the peaks (i.e. peak area) are nearly identical, strongly suggesting the observed data is indeed from water, which

[66] Talley, A. D., Rogers, B. R., Iakovlev, V., Dunn, R. F., Guelcher, S. A. "Oxidation and degradation of polypropylene transvaginal mesh." *J. Biomat Sci, Poly Ed*, (2017) Online Only: 1-15.

most likely persisted from insufficient drying of the specimen. Unnecessarily confounding the analysis even further, the authors chose to truncate the spectral data by not displaying or presumably analyzing the entire mid-IR region (4000 to 400 wavenumbers).[67,68] Had the authors performed a complete IR analysis, the presence of water could have been confirmed or ruled out by examining the spectra for a third characteristic peak at ~690 cm^{-1}. Having not done so renders this work, at best, incomplete and, at worst, highly dubious. In either case, the interpretation of the partial data does not meet the minimal scientific standards to form the basis for a conclusive or reliable opinion regarding oxidation of the analyzed sample.

[67] Chalmers, J. M. "Infrared Spectroscopy in Analysis of Polymers and Rubber." *Infrared Spectroscopy In Analysis Of Polymers And Rubbers.*(2006) Encyclopedia of Analytical Chemistry, pp.1.

[68] Sibilia, J. P., *A Guide to Materials Characterization and Chemical Analysis.* USA, 1988, pp.13-14.

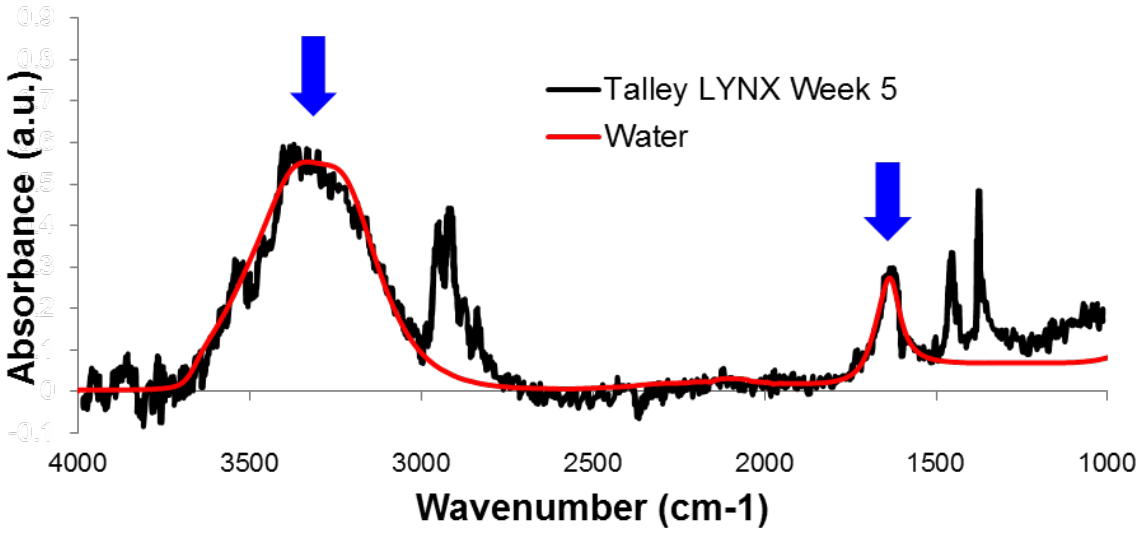

Figure 5. An overlay of FTIR spectra of LYNX mesh after 5 weeks of exposure to an oxidative medium reported by Talley[66] and deionized water. The blue arrows correspond to the peak positions expected by Talley to correspond to signals for a hydroxyl functional group (left arrow) and a carbonyl functional group (right arrow). The two spectra have been rescaled in the y-axis to match their relative intensities. The spectrum published by Talley *et al.* was digitized using Webplot Digitizer software. The deionized water (source: PTI Process Chemicals, Filled: April '2013' B, purchased from McMaster-Carr Supply Company) spectrum was collected using a model 6700 Nicolet infrared spectrometer equipped with a DLaTGS detector, KBr beam splitter and employing a Smart Orbit diamond, single-bounce, attenuated total reflectance (ATR) accessory (Thermo Electron Corporation, Madison, WI). The reported spectrum is the average of 128 sequentially collected spectra across a range of 4000 - 525 cm^{-1} acquired at a resolution of 4 cm^{-1}.

Second, the authors appear to have swapped the peak area plots for the two functional groups in Figures 2B and 2C. These plots purportedly denote the peak areas for each mesh over the duration of the experiment. However, the functional groups assigned in the captions to these figures are incorrect. Assuming the data in the figures are correct, Figure 2B should correspond to the hydroxyl peak data and Figure 2C should correspond to the carbonyl peak area, not vice versa as the authors have reported. Such a fundamental, yet substantial error brings into question the quality and thoroughness of the authors' protocols and methods for data recording and analysis.

Notwithstanding the errors cited above, the authors peak area results are meaningless given the relatively subtle nature of the bands of interest in comparison to the appreciable signal to noise ratio in the overall spectra. In light of the appreciable signal to noise ratio, the authors rely on the use of a manual baseline correction to complete their analysis. Although not addressed by the authors, this technique lends itself to potential sources of error. For instance, the example Week 1 FTIR spectrum plotted for TVT has a visually similar hydroxyl band (3600 – 3050 cm^{-1}) to that of Week 5 (dashed lines in Figure 6); but the authors only identify significant hydroxyl and carbonyl peaks in the Week 5 spectrum. A manual baseline correction may or may not bring the hydroxyl peak into statistical significance, but the manual aspect of the correction minimizes, if not negates, the value of the statistical analysis. It is also unclear as to why the Week 1 TVT hydroxyl data was not considered statistically significant.

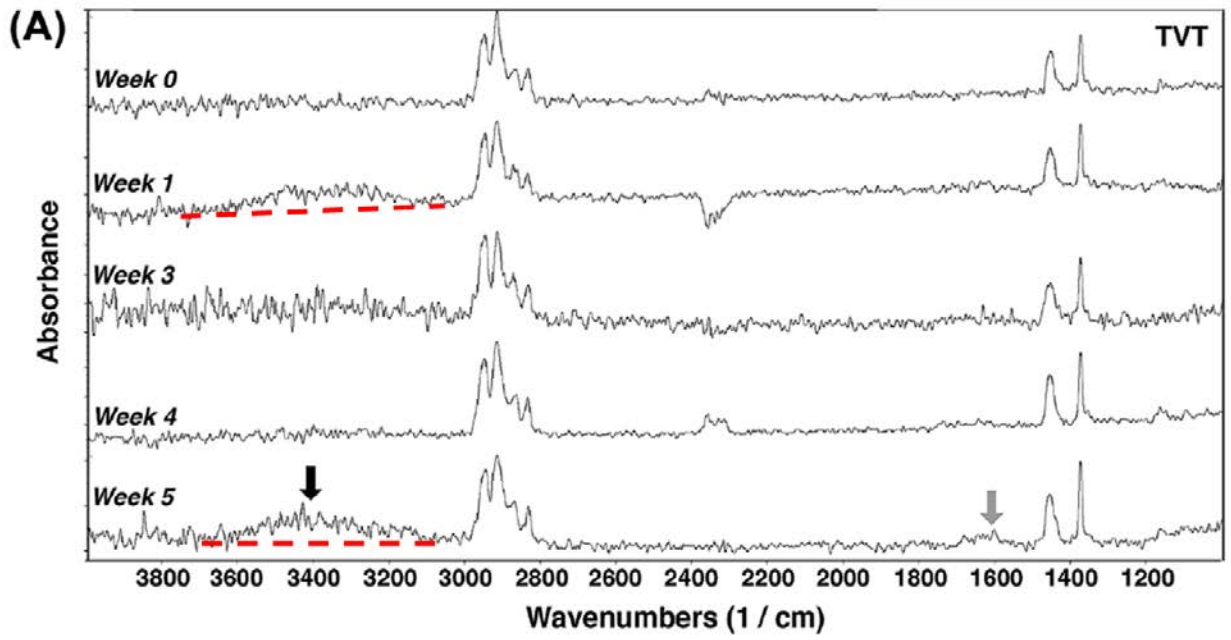

Figure 6. FTIR data of TVT taken from Talley 2017. Red dashed lines were added as a guide.

Additionally, semi-quantitative analysis (i.e. comparison of like samples) based on FTIR data such as Talley's Figure 2B and C requires that the relative intensities of the data are appropriately scaled so that any peak area comparisons can be appropriately made. Examples of

this in practice include adding an internal calibration standard into the sample or rescaling the data to a known, fixed intensity/area peak (e.g. CH_x band at ~2900 cm^{-1}). It is unclear how/if the authors rescaled the data based on the lack of details put forth in the publication. Lack of such details do not allow for an appropriate level of reproducibility of their work which, once again, is a standard within the scientific community.

Talley attempts to quantify oxidation by integrating the so-called carbonyl peak range in the IR spectrum between 1750 and 1500 cm^{-1}. However, these unsubstantiated limits of integration are erroneous. Per authoritative IR spectroscopy reference literature, the scientifically accepted range for carbonyls is 1850 to 1580 cm^{-1}, with the exception of carboxylate salts that can resonate at 1610-1550 cm^{-1}.[69,70] Since carboxylate salts are not byproducts of any alleged polypropylene oxidation mechanism, the lower limit for any type of integration in the carbonyl range would remain at 1580 cm^{-1}, not 1500 cm^{-1}.

Based on Talley's alleged oxidation mechanism, other evidence of hydroperoxide groups should be observable by FTIR, and should be noted in this analysis as the hydroxyl peak is ubiquitous to several functional groups and compounds (including water). The authors could have utilized the oxygen-oxygen single bond vibrational stretch at ~845 cm^{-1} or the peak from the COO linkage around 525 cm^{-1} towards proof of the presence of hydroperoxide.[71] Neither of these peaks were noted.

The authors also studied the surface appearance before and after exposure to the oxidative medium using SEM. Flaking, peeling, and pitting was observed on the surface of TVT mesh after 5 weeks. The visual appearance reported in this study is completely inconsistent with the morphology of explanted polypropylene mesh samples (i.e. transverse cracks). The authors note

[69] Lambert, J.B., *Introduction to Organic Spectroscopy*, Macmillan, NY, 1987, pg. 174-177.

[70] Coates, J., *Interpretation of Infrared Spectra, A Practical Approach*, John Wiley & Sons, Chichester, UK, 2000, pg. 12-13.

[71] Bernal, H. G., Caero, L. C., Finocchio, E., Busca, G. "An FT-IR study of the adsorption and reactivity of tert-butyl hydroperoxide over oxide catalysts." *Appl. Cat. A: General*., (2009) 369:27-35.

this discrepancy and claim that mechanical strain is also needed to recreate the morphology of explanted polypropylene mesh samples. However, this explanation is nothing short of pure speculation and inconsistent with the observed cracking in non-mechanically strained, intentionally QUV-oxidized samples outlined later in this report (section entitled "Exponent Investigation into Staining of Intentionally Oxidized PROLENE Mesh"). Moreover, to confirm their belief that the combination of stress and a contrived *in vitro* oxidation environment is required to induce transverse cracking, Talley could have easily added a component of stress into their experiment. No such effort was made by the authors. Furthermore, the FTIR band attributed to carbonyl functionality in Talley's *in vitro* oxidation study is centered at 1650 cm^{-1}, while the carbonyl bands in explants reported in studies cited by Talley[57,83] fall between 1700-1750 cm^{-1}. In short, the authors were clearly unable to replicate an authentic *in vivo* environment in their study as evidenced by the gross differences in surface morphology and carbonyl peak position between test specimens and patient explants. As such, any conclusions or opinions related to *in vivo* oxidation of PROLENE derived from this study are scientifically baseless.

The authors also investigated changes to an explanted American Medical Systems (AMS) polypropylene midurethral sling by X-ray photoelectron spectroscopy (XPS). The explanted sample analyzed with XPS was not fixed in formalin, but since no details about cleaning or preservation were disclosed, it is assumed that no solvent washing was performed. Select fibers were also scraped, to an arbitrary depth, using a tweezers and scalpel to purportedly remove "adherent tissue without disturbing the underlying layer of oxidized PP." XPS was utilized, in part, to identify two functional groups (carbonyl and hydroperoxide) that were claimed to be found as a result of polypropylene oxidation. As discussed in detail below, the authors misunderstood the literature they cited and misinterpreted the results in ways that render their conclusions meaningless.

As a matter of first principles of organic chemistry, the authors have mistakenly conflated two distinctly different COOH isomers in their analysis, namely hydroperoxides and carboxylates. They opine in the body of the article that the presence of hydroperoxides is an indication of

polypropylene oxidation. The text of the article refers to peaks at ~287 eV as hydroperoxide peaks, but in the XPS figure (Figure 4D[66]) they label this same peak as a carboxylate (see Figure 7).

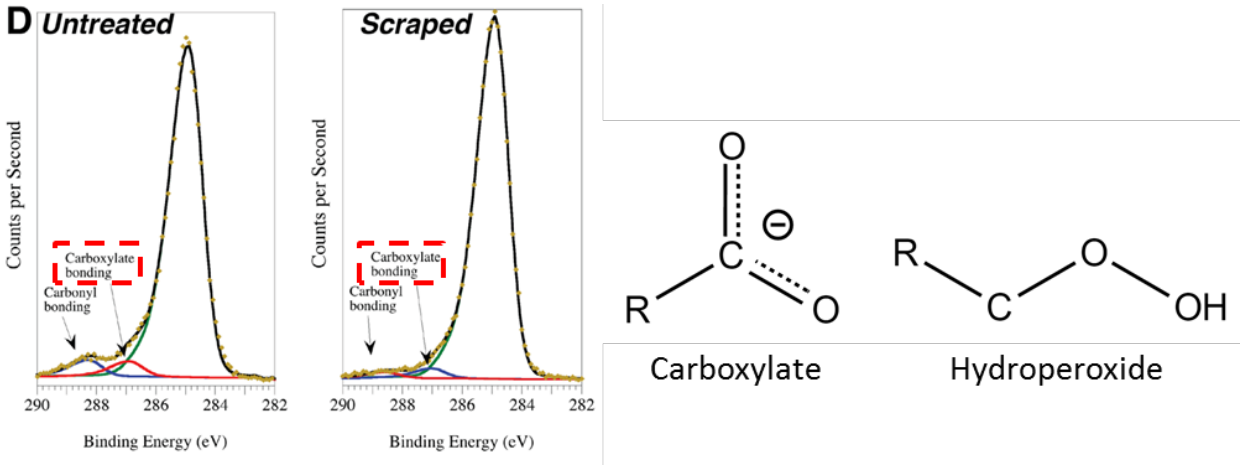

Figure 7. (Left) XPS data (figure 4d) from Guelcher 2017. Red boxes were added as a visual guide. (Right) Chemical structures of two isomeric functional groups.

Talley also claimed a mechanism for polypropylene oxidation that terminates with the formation of a carbonyl functional group through a stable hydroperoxide intermediate. The authors contended that this reaction intermediate is detectable, and claim its presence as proof of oxidation. However, according to the authors' own reference, hydroperoxides are *highly unstable* and readily decompose into other byproducts.[72] Thus, the presence of stable hydroperoxides should not be expected as a result of polypropylene oxidation.

There are also clear and convincing signs of sample contamination with Talley's XPS data that may have significantly skewed the study's results. Specifically silicon was detected in 9 of the 15 samples analyzed by XPS, with the maximum observed content being 3% of the total atomic composition (Table S1). Talley provides neither an explanation for the presence of silicon, nor its wide variation in the collected data. Although no formulation details of the examined AMS mesh materials are provided by the authors, it is highly unlikely that silicon or silicon containing

[72] Kausch, H. H., "The effect of degradation and stabilization on the mechanical properties of polymers using polypropylene blends as the main example." *Macromol. Symp.* (2005) 225:165-178.

compounds are constituents of polypropylene-based mesh. Of course a control experiment, which the authors chose not to perform, could have confirmed the lack of silicon in an exemplar mesh sample. In any case, there is no silicon present in human tissue.[73] However, silicon is a common laboratory contaminant, as it is a major element in silicone greases and lubricants that are routinely used to maintain laboratory instruments including XPS.[74] Silicone also contains at least the same amount oxygen as silicon. Since silicones are oxygen containing, the presence of silicone contamination would artificially inflate the relative percentages of oxygen to carbon detected by at least the same percentage as the amount of silicon detected. If the contaminant is indeed silicone, then the tabulated data is incorrect rendering any related conclusions suspect.

Talley's peak deconvolution of the C 1s band contains its own issues. Given the high level of peak overlap that is present in their data, lax constraints on parameters used for deconvolution, such as peak position, width or number of curves, are ill-advised since they do not provide a high level of confidence for sample comparisons. Talley does not detail the peak deconvolution parameters used, but from the figures in the supporting information it is apparent that the proper and consistent constraints were not used. For example, there appears to be no consistency in the number of peaks used to deconvolute the data. The peak centered at ~284.3 eV (which is not assigned a functional group) is used in the deconvolution analysis in 6 of the 15 samples analyzed, without any accompanying explanation for why some samples are analyzed differently than others. Most of the samples with this peak identified are at concentrations at or below 1.0%, including one sample reported to have 0.0% of this unidentified carbon bond. The distinction between 0.0% and not detected was not detailed by the authors and the relevance of these low values are suspect given that the standard deviation (1.5%) is substantially larger than the concentrations calculated. Furthermore, relative amounts above 1.0% of this peak were only observed in 1 fiber (fiber 17) suggesting this peak is due to an unidentified material, not polypropylene or oxidized polypropylene. Conclusions drawn from this data are suspect in part due to this analysis procedure.

[73] Kim, Y. S. "Human Tissues: Chemical Composition and Photo Dosimetry Data." Radiation Research, (1974) 57(1):38-45.

[74] https://www.cemag.us/article/2004/03/silicone-contamination-part-1, Accessed 6-7-17.

Talley's XPS data is also rife with computational, statistical and data acquisition errors. For example, according to the scraped fiber data set in Table S6 of the supplemental data, carboxylate (R-C*COOH) concentrations of 2.5% and 2.3% were found on the scraped surfaces of Fibers #5 and #8, respectively. The concentrations were reportedly based on binding energies from the XPS data at approximately 287 eV. However, upon careful review of the spectral data shown in Figure S2 of the Talley article, no peaks are present at 287 eV for Fibers #5 and #8. Similarly, although the carbonyl peak was identified in the spectra for Fibers #5 and #8, no values were recorded in Table S6. These obvious and unexplained discrepancies cast serious doubt as to the authenticity and veracity of the entire XPS data set. To the extent it is argued that the relatively low concentration of carboxylate compounds leads to subtle peaks that are difficult to discern in the plotted XPS spectra, that argument is debunked by simply comparing the data and spectra of Fiber #23 to Fibers #5 and #8. For Fiber #23, a carboxylate concentration of 2.6% is noted in Table S6, yet its corresponding peak at 287 eV is clearly visible in the corresponding spectrum in Figure S2. In addition, the atomic percentages in Fiber #9 in Table S4 sum up to over 100% (104.8%), which is both illogical and scientifically invalid. Moreover, several of the mean and standard deviation values computed throughout the tabulated data are incorrect and many of the standard deviations are substantially larger than their corresponding mean values, creating nonsensical negative values in the overall spread of the data.

Finally, the authors misinterpreted the results of the survey and high resolution C 1s XPS data gathered on the explanted sample. The surface of the fiber was mechanically scraped in an attempt to remove adherent tissue. However, the authors did not describe the scraping technique employed, leaving other researchers, some of which may wish to reproduce this work, to guess at the applied scraping force, degree of scraping and achieved material removal. Such ambiguity is inconsistent with the scientific method. Subsequent to scraping, the authors claimed proteinaceous material was no longer present and theremaining detected oxygen was solely due to oxidized polypropylene. However, the authors neglected to account and test for other oxygen containing molecules that are likey present from the *in vivo* environment. First, oxygen containing (and nitrogen free) fatty acid esters and cholesterol have been previously reported to

diffuse into the fibers *in vivo*.[75,76] Second, the authors did not discuss or determine the chemical components used in AMS's polypropylene formulation. From a commercial resin standpoint, it is quite possible that one (or more) of the additives used in AMS's polypropylene resin contains oxygen in its chemical structure. Third, the authors made repeated mention of "reactive oxygen species" (ROS) secreted by adherent inflammatory cells present in the *in vivo* environment. Given the authors provided no information on cleaning steps, it is possible these ROS persist on the surface of the fiber, and contribute to the oxygen signal. All of these points could have been addressed through the analysis of any number of control samples, none of which were used in this study. In short, control AMS samples should have been incorporated into this study. They were not and their omission taints the validity of any related findings. Additionally, much of this confusion could have been eliminated if the authors had investigated the O 1s band instead of the C 1s band.[77] Oxygen-oxygen single bonds are likely to be more easily distinguished from other oxygen containing functionalities during peak deconvolution. Their failure to do so underscores their lack of expertise using this technique.

It is also worthwhile to note the inconsistent analytical approaches taken throughout the course of the study. Specifically, Talley utilized FTIR to identify chemical functional groups associated with the outer surface of mesh fibers that were incubated for five weeks in a peroxide-based oxidative medium. However, XPS was employed to characterize C 1s binding energies associated with the surface of an explanted AMS mesh. As previously cited in this report, FTIR reflectance techniques typically survey material surfaces to depths on the micron scale (10^{-6} meters),[46] whereas, XPS surveys material surfaces to depths on the order of nanometers (10^{-9} meters).[78] The authors provide no explanation as to why two separate techniques, with different

[75] Bracco, P., Brunella, V., Trossarelli, L., Coda, A., Botto-Micca, F., "Comparison of polypropylene and polyethylene terephthalate (Dacron) meshes for abdominal wall hernia repair: A chemical and morphological study." *Hernia*, (2005) 9(1):51-55.

[76] Jordi Wave 1 Case Report dated 2-1-16, Exhibit B, pg. 66.

[77] Dilks, A., "The Identification of Peroxy-Features at Polymer Surfaces by ESCA." *Journal of Polymer Science: Polymer Chemistry Edition*, (1981) 19:1319-1327.

[78] Skoog, D. A., Holler, F. J., Nieman, T. A. *Principles of Instrumental Analysis Fifth Edition.* USA: Thomson Learning, 1998.

capabilities and sensitivities, were employed to purportedly equate the oxidative response of mesh exposed to contrived *in vitro* conditions and *in vivo* conditions. The lack of synergy between the disparate approaches and data sets confounds the study to the point where meaningful scientific comparisons cannot be made.

Given that the Tally article lacks proper controls and is fraught with errors, omissions and inconsistencies, the work fails to meet the bar of the scientific method and, therefore, its findings are unreliable. As such, any opinions formed as a result of these findings are also unreliable. Notwithstanding the numerous shortcomings described herein, the Talley work, at most, is simply a recitation of ill-considered findings that have been circulating in the literature for the past decade. Talley has reportedly identified ubiquitous IR and XPS peaks that are associated with a multitude of oxygen containing molecules, many of which are present *in vivo*, and has solely ascribed those peaks as evidence of *in vivo* oxidation of polypropylene. In addition, the authors have blindly adopted Zhao's oxidative medium by not appreciating Zhao's study was dependent on material type and material-specific damage and was not proven to be scalable to multiple explanation times. As such, no meaningful comparisons can be made between Talley's intentionally oxidized specimens and the alleged *in vivo* oxidation of PROLENE mesh.

Kurtz

Kurtz *et al.*[79] examined the tensile strength of Ethicon's ULTRAPRO mesh after six months of exposure to varied concentrations of hydrogen peroxide solution. According to Kurtz, 500 µM of reactive oxygen species (ROS) have been reported in the serum of human adults. The researchers elected to use hydrogen peroxide as the representative ROS due to its "role in inflammation," and performed tensile testing on mesh samples after six months of exposure in 0 M, 1 mM, 0.1 M, and 1 M solutions. The study also included SEM of fracture surfaces of 0 M

[79] Kurtz, J., Rael, B., Lerma, J., Wright, C., Khraishi, T., Auyang, E.D. "Effects of reactive oxygen species on the physical properties of polypropylene surgical mesh at various concentrations: a model for inflammatory reaction as a cause for mesh embrittlement and failure." *Surgical endoscopy,* (2015) : 1-6.

and 1 M exposed fibers after tensile testing. Kurtz found that six months of exposure to 1 mM and 0.1 M solutions resulted in an approximately 30% decrease in tensile strength, and that samples exposed to 1 M solutions exhibited qualities of "extreme embrittlement."

ULTRAPRO mesh is constructed with a different fiber composition and knit structure than PROLENE mesh. The composition of ULTRAPRO is of great significance in the interpretation of this study because the mesh is manufactured with equal parts absorbable MONOCRYL poliglecaprone-25 monofilaments and non-absorbable PROLENE polypropylene-based monofilaments.[80,81] After absorption of the MONOCRYL filaments, the PROLENE filaments remain.[80] Kurtz made no attempt to determine the degree to which MONOCRYL filaments were present within the mesh at the time of testing, which could have a significant effect on the tensile strength of the mesh.

In contrast to Ethicon's Seven Year Dog Study, tensile testing performed by Kurtz showed the expected trend for an oxidized polymer. The elongation at break for samples exposed to 1 mM and 0.1 M hydrogen peroxide stayed within one standard deviation of the 0 M control samples, and the samples exposed to 1 M hydrogen peroxide showed a decrease in elongation at break. The PROLENE sutures examined in the Seven Year Dog Study exhibited an *increase* in elongation at break, suggesting that the polymer undergoes plasticization, rather than oxidation.

SEM was performed on samples exposed to 0 M and 1 M hydrogen peroxide. According to Kurtz, only 500 µM (0.5 mM) of ROS was reported in the serum of human adults; therefore, the 1 M samples were exposed to a more extreme environment than expected in the human body. Even so, the "cracks" observed in other studies were not observed here.[82] Rather than showing a

[80] Pott, P., Schwarz, M., Gundling, R., Nowak, K., Hohenberger, P., Roessner, E. "Mechanical properties of mesh materials used for hernia repair and soft tissue augmentation." *PloS One*, (2012) 7(10):e46978.

[81] Chowbey, Pradeep, ed. Endoscopic Repair of Abdominal Wall Hernias (2nd Edn.): Revised and Enlarged Edition. Byword Books Private Limited, 2012.

[82] Kurtz *et al.* stated that "[s]tress cracking was difficult to observe due to gold/palladium coating and limitations in resolution". This statement stands in contrast to scanning electron microscopy images taken at similar magnifications with visible "cracks" (See Clavé, de Tayrac, Cozad, Mary, Wood).

series of images at increasing magnifications to provide context as to where the fiber failed within the knit fabric structure, the researchers elected to show only one image of a failed fiber. The fracture surface images were taken at different magnifications, 650X and 1500X for the 0 M and 1 M samples, respectively, and are therefore misleading. The "brittle" fiber exposed to 1 M hydrogen peroxide has a diameter (75 µm) that is 20 µm smaller than the "non-brittle" fiber (95 µm) exposed to a 0 M environment. By the authors' own admission, ROS concentration does not exhibit a linear relationship with changes in mechanical properties. Regardless of the numerous misgivings in the study, Kurtz ultimately illustrated the expected tensile property trends for an oxidized polymer. All of these trends run counter to the findings in Ethicon's Seven Year Dog Study and suggest that *in vitro* experiments may not accurately represent end-use, *in vivo* conditions.

Bracco

Bracco *et al.*[75] studied twenty-five explanted polypropylene and polyethylene terephthalate (PET) hernia meshes from undisclosed manufacturers. The time spent *in vivo* varied from 2 to 52 months for polypropylene meshes, and from 36 to 180 months for PET meshes. Explanted samples were stored in a 4% formalin solution, cleaned for 24 hours in a NaOCl solution, and rinsed with distilled water.

FTIR spectra of the cleaned polypropylene explants exhibited a consistent absorption band in the carbonyl region at 1728 cm^{-1}. In contrast to other studies,[45,53,58,59] Bracco did not assume that this peak was evidence of oxidation, and performed additional experiments to determine its origin. The researchers repeated the FTIR analysis after subjecting the explants to a 24 hour cyclohexane extraction to remove any foreign molecules which may have been adsorbed by the polypropylene material while *in vivo*. The results showed that the explants no longer exhibited the carbonyl functionality observed prior to the extraction, but the cyclohexane extraction solvent did. Gas chromatography-mass spectroscopy (GC-MS) performed on the cyclohexane extracts found evidence of squalene, palmitic acid, cholesterol, stearic acid, and other unidentified substances. Some of these substances, including palmitic and stearic acids, contain

carbonyl containing functional groups that most likely contributed to the observed carbonyl functionality observed in both the explanted polypropylene meshes and the cyclohexane extracts. Based on this analysis, Bracco concluded that carbonyl functionality in explanted polypropylene mesh "does not arise from a chemical modification of PP due to its stay in the human body," but rather from a "chemical species present in the human tissues that have been transferred to the polymer." It is worth noting that these findings are consistent with Dr. Jordi's pyrolysis mass spectrometry (PYMS) study[76] where he was able to extract similar carbonyl-containing aliphatic species from explanted meshes.

Imel

Imel *et al.*[83] studied the chemical and molecular weight characteristics of Boston Scientific (not PROLENE) Pinnacle meshes before and after implantation in the human body. After explantation, all meshes were stored in formalin until the study was implemented. SEM and energy dispersive X-ray spectroscopy (EDS) were performed on exemplar and uncleaned explanted meshes, while FTIR of explanted meshes was performed only after a 24 hour soak in a sodium hypochlorite cleaning solution.

FTIR spectra were presented for two exemplar mesh controls, as well as four explanted meshes that had been cleaned in a sodium hypochlorite solution. The study claimed that the carbonyl absorbance bands visible on the explanted samples between 1700 and 1750 cm^{-1} offered clear evidence of oxidation. However, the researchers failed to acknowledge the significance of the amide II peak at 1550 cm^{-1}, typically indicative of the presence of residual tissue, which was visible in three of the four explanted specimens. As mentioned previously, amide bonds are inherent to proteins which contain both amide and carbonyl functionality. In addition, Imel cited observations made by Bracco *et al.*[75] that small molecules (e.g. esterified fatty acids) with carbonyl functionality have the potential to be absorbed into the mesh material. Given the

[83] Imel, A., Malmgren, T., Dadmun, M., Gido, S., Mays, J. "*In vivo* oxidative degradation of polypropylene pelvic mesh." *Biomaterials*, (2015) 73:131-141.

presence of residual tissue and small molecule fatty acid esters, it is impossible to attribute the presence of carbonyl functionality solely to oxidation.

Imel also showed SEM images and EDS spectra of control and explanted mesh specimens. EDS was used to determine the elemental composition of the fiber and the fiber surface, and Imel claimed that because nitrogen is found in proteins, the observed presence of oxygen with an absence of nitrogen on an explanted Boston Scientific mesh suggested oxidation. The problem with this logic is twofold. First, as indicated by the researchers, many of the EDS spectra for explanted mesh (both of "clean fiber" and on "biomaterial coated fiber") showed some presence of both nitrogen and oxygen. This is evidence that the tissue on the "clean fiber" region has not been fully removed and therefore the continued presence of biological material explains the oxygen detected in the EDS spectra. Secondly, Bracco *et al.*[75] showed that small oxygen containing molecules are adsorbed into the mesh material while *in vivo*, and would be expected to contribute to the EDS spectra. In short, the presence of oxygen, either with or without nitrogen, is expected as a result of the residual tissue and small oxygen containing molecules which have been adsorbed into the mesh material.

Imel analyzed the molecular weight and polydispersity index (PDI) of Boston Scientific Pinnacle control and explanted meshes. The researchers claimed to see a reduction in both the molecular weight and the PDI of explanted mesh when compared to control mesh. It is interesting to note that, when comparing FTIR spectra of the same explanted mesh, the presence of carbonyl functionality does not necessarily correlate with the purported reduction in molecular weight, as would be expected if the mesh were oxidized. For example, the FTIR spectra of explant XP-7 showed minimal carbonyl functionality (even with the presence of fatty acid esters, as reported by Bracco), yet displayed an alleged reduction of 44,000 daltons in molecular weight and a 2.02 reduction in PDI. A reduction in molecular weight and PDI of this magnitude is expected to coincide with substantial carbonyl functionality observed by FTIR. The fact that this was not observed calls into question the validity of the controls.

Finally, it is important to restate that Imel performed all testing on Boston Scientific explanted mesh, not on Ethicon's PROLENE mesh. Although the study reports an alleged reduction in molecular weight after implantation, similar studies performed on Ethicon's PROLENE material showed no reduction in molecular weight with implantation time.[84,85]

Thames

Thames *et al.*[86] investigated 78 explanted PROLENE-based meshes used to treat stress urinary incontinence (SUI) and pelvic organ prolapse (POP). The explanted meshes had implantation durations of 0.4 to 11.7 years. According to the authors, other studies involving explanted polypropylene meshes alleged *in vivo* oxidative degradation of polypropylene meshes based on the presence of a cracked morphology on the surface of the explanted meshes and a very small sample size. However, according to Thames, these other studies did not fully clean the explants of biological material, resulting in incomplete analysis. The well-known fixation (crosslinking) reactions between formalin and proteins cause tissue to strongly adhere to implanted mesh, preventing easy cleaning of the biological material.

In order to reverse the fixation reactions and properly clean the explants, Thames *et al.* soaked the meshes in distilled water at elevated temperatures (70^{o}C-80^{o}C) followed by treatment and/or ultrasonification with solutions containing 10-15% NaOCl or the enzyme Proteinase K. The water soaks aided in reversing the protein fixation facilitated by formalin while the NaOCl and Proteinase K treatments removed bulk tissue and biological deposits surrounding the fibers. Explanted meshes were evaluated iteratively throughout the cleaning procedure by optical microscopy, SEM and μATR-FTIR.

By employing their cleaning protocol on a series of explanted PROLENE mesh samples, Thames *et al.* concluded that PROLENE meshes do not oxidize *in vivo*. The crust, as described

[84] Ethicon's Seven Year Dog Study (ETH.MESH.09888218 – 09888222) pg.146-150.

[85] Wave 1 General Expert Report of Howard Jordi Report-2-1-16.pdf., Exhibit A_Jordi Lewis Report

[86] Thames, S.F., White, J.B., Ong, K.L., The myth: in vivo degradation of polypropylene-based meshes. International Urogynecology Journal (2017) 28:285-297.

in other literature sources as potentially oxidized polypropylene, was present at the initial stages of the cleaning, but was progressively removed throughout the cleaning process as shown by optical microscopy and SEM. Furthermore, FTIR data showed that as cleaning progressed, protein absorbance peaks in the 3,300 cm^{-1} region (N-H amide stretch), and peaks in the region of 1,600–1,690 cm^{-1} (amide I stretch) continually decreased, indicating the presence and subsequent removal of residual proteinaceous material on the cracked outer surfaces of the explanted mesh samples. Oxidized polypropylene would not be expected to show absorption peaks in these areas; therefore, the removal of these peaks indicates that the mesh was not oxidized but instead coated with a removable layer of biological material.

Ethicon's Investigation

In the course of its investigation, Exponent has reviewed a series of internal Ethicon documents detailing experiments conducted on explanted sutures in the 1980's.

Microcrack Committee Investigation

Ethicon conducted experiments to investigate alleged cracking observed on the outer surface of explanted PROLENE sutures in the 1980s. As part of their internal investigation, Ethicon formed a "microcrack committee" of scientists that carried out multiple experiments including various forms of microscopy, mechanical testing, melting point analysis, and FTIR analysis on both explanted materials and intentionally oxidized controls to understand the composition of the observed cracked layer on the outer surface of explanted PROLENE sutures. The studies performed by this committee contain test reports, internal Ethicon memos, and correspondence among Ethicon staff, scientists, and surgeons.

Microscopy

Ethicon's scientists examined numerous uncleaned explanted PROLENE sutures by both optical microscopy[87,88,89,90,91] and SEM,[47,90,91] confirming an outer cracked layer on some of the explants. Further microscopic examination was performed using cross-polarized light microscopy to determine if exemplar PROLENE sutures exhibited a core/shell morphology

[87] 14 – "Examination of 5/0 and 6/0 Cardiovascular PROLENE Sutures Explanted after 2 to 6 Years Implantation" memo 1983.03.25 (ETH.MESH.15958410-58432).

[88] 15 – "Human Retrieval Specimens from Dr. Roger Gregory, Norfolk Surgical Group" memo 1983.03.29 (ETH.MESH.15955440-15955442).

[89] 19 – "Examination of PROLENE (Polypropylene) Sutures from Human Cardiovascular Explants" memo 1984.05.02 (ETH.MESH.15955462-15955468).

[90] 23 – "PROLENE Microcracking" memo 1984.11.05 (ETH.MESH.15958452-15958469).

[91] 24 – "PROLENE Polypropylene Suture Explant from Dr. Drewes" memo 1984.11.07 (ETH.MESH.15958405-15958407).

associated with variations in crystallinity resulting from the manufacturing process. It was found that there was "no indication of a gross skin feature on PROLENE sutures."[90]

Using transmission electron microscopy (TEM) in diffraction mode[90] to examine an explanted cross-section further confirmed the presence of a semi-crystalline inner core material, and an *amorphous* cracked outer layer, suggesting the cracked outer layer was not PROLENE.

Mechanical Testing

Tensile testing was performed by Ethicon's scientists on explanted PROLENE sutures of various sizes that were "relatively free from instrument damage"[88] and compared with exemplar sutures of similar sizes to determine the change in breaking strength. Explanted sutures exhibited breaking strengths ranging from 47%–110%[92] of the values obtained for their representative control sutures.[88,89] The elongation at break and modulus were not reported in this study and therefore it is impossible to determine if the reported reduction in breaking strength is a result of material degradation, or simply an *in vivo* plasticization effect as seen in the Seven Year Dog Study, which will be discussed in detail later.[51]

Melting Point Analysis

In a further effort to identify the composition of the cracked outer film on explanted PROLENE sutures, Ethicon investigated the melting point of the exterior layers. Explanted sutures were heated, resulting in contraction and peeling of the outer cracked surface layer. The suture and peeled layer were further heated until the bulk PROLENE suture had melted (~165°C). In most cases, the bulk fiber melted first "but the crack (sic) layer maintains its form,"[90] indicating that the cracked layer is not degraded PROLENE, which would have a *lower* melting temperature than bulk PROLENE. Ethicon repeated these melting point experiments with protein serum coated exemplar sutures with analogous results, stating that this "protein layer has similar

[92] Of the 13 sutures tested, 12 exhibited breaking strengths 75% or higher of values obtained for their representative control sutures.

characteristics to the crack layer on explants in that it separates from the fiber cleanly with heating and maintains its form after the PROLENE fiber has melted."[90]

FTIR Analysis

FTIR is a technique used to identify particular chemical bonds present in a sample and to identify specific polymer types. Ethicon performed FTIR analysis of the cracked outer layer, bulk explanted sutures, intentionally oxidized controls, protein immersed controls, and exemplar PROLENE sutures to determine the composition of the cracked outer layer by the functional groups present in each type of sample.[90,93,94] As discussed previously, carbonyl containing functional groups are formed upon oxidation of polypropylene and are typically associated with absorption peaks between approximately 1650 cm^{-1} and 1810 cm^{-1} in the FTIR spectrum.[8,95,96] Interpreting the FTIR spectra obtained by Ethicon is non-trivial due to a multitude of factors. Characteristic functional groups in proteins,[93] DLTDP (antioxidant),[94] formaldehyde cross-linked proteins,[14] fatty acid esters,[97] and oxidized polypropylene[94] (Figure 8) include carbonyl groups, which confound the interpretation of FTIR spectra generated from explanted meshes and sutures manufactured from PROLENE.

[93] 25 – "Fourier Transform-Infrared Examination of PROLENE Microcrack and Photo-Oxidized Polypropylene" memo 1984.11.13 (ETH.MESH.15958336-15958395).

[94] 28 – "IR Microscopy of Explanted PROLENE Received from Prof. R. Guidoin" memo 1987.09.30 (ETH.MESH.12831391-12831404).

[95] Carlsson, D. J., Wiles, D. M. The Photodegradation of Polypropylene Films. III. Photolysis of Polypropylene Hydroperoxides. *Macromolecules*, (1969) 2(6):597–606.

[96] George, G. A., Celina, M., Vassallo, A. M., Cole-Clarke, P. A. Real-Time Analysis of the Thermal Oxidation of Polyolefins by FT-IR Emission. *Polym. Degrad. Stab.*, (1995) 48(2):199–210.

[97] Movasaghi, Z., Rehman, S., ur Rehman, D. I. "Fourier Transform Infrared (FTIR) Spectroscopy of Biological Tissues." *Appl. Spectrosc. Rev.*, (2008) 43(2):134–179.

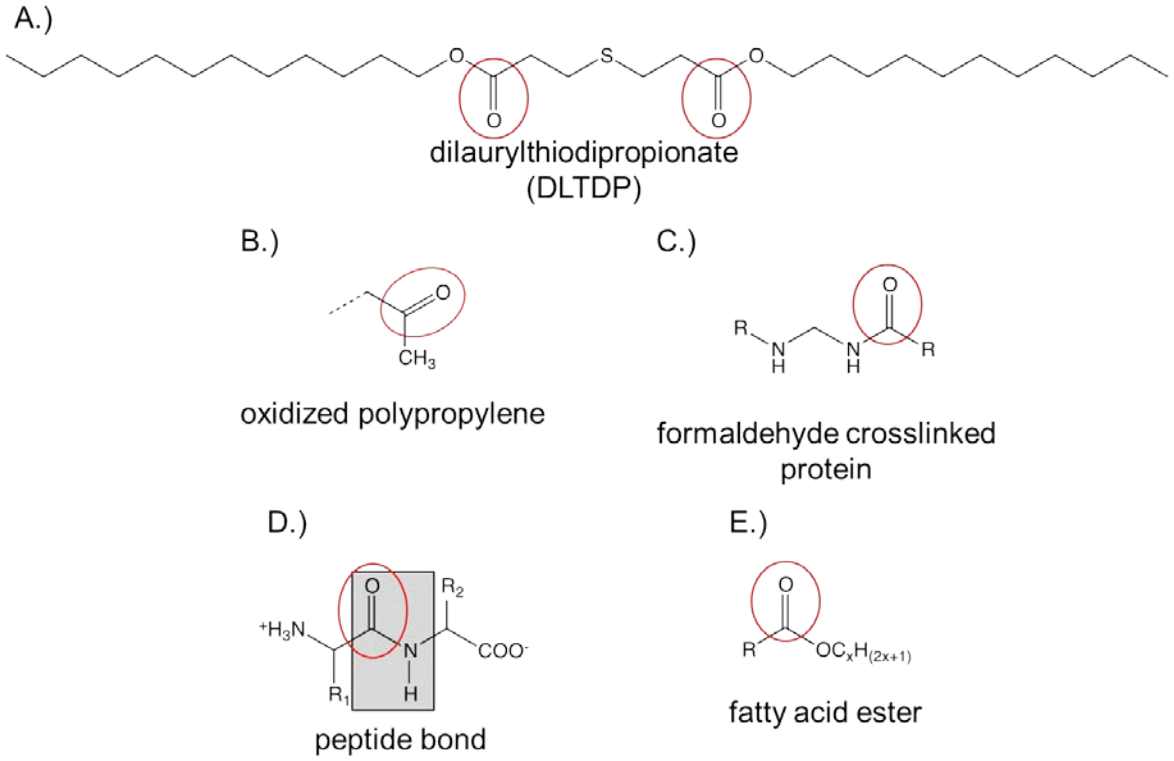

Figure 8. A.) Chemical structure of dilaurylthiodipropionate[98], B.) oxidized polypropylene[1], C.) formaldehyde crosslinked proteins[14], D.) a peptide bond, which make up proteins[99] and E.) a fatty acid ester[97]. All of these molecules have functional groups which contain carbonyls (circled in red).

Ethicon performed studies that included FTIR spectroscopy of intentionally oxidized polypropylene and PROLENE samples that were immersed in protein serum.[93] Studies involving intentional oxidation, such as hot pressed samples and photo-oxidized induced samples, showed consistent carbonyl peaks in the 1720 cm^{-1} region. Explanted samples and non-explanted samples immersed in protein serum inconsistently showed peaks in the 1700 cm^{-1} to 1740 cm^{-1} region, indicating oxidation was unlikely to be the contributing factor to the peaks. Rather, carbonyl or other oxygen containing groups from the serum or *in vivo* conditions contributed to the observed peaks.

[98] Chemical Book, accessed August 23, 2015. http://www.chemicalbook.com/ChemicalProductProperty_EN_CB3712869.htm

[99] Godbey, W. T. *An Introduction to Biotechnology the Science, Technology and Medical Applications.* Woodhead Publishing, 2014.

Seven Year Dog Study

Study Protocol

As part of the microcrack committee, Ethicon initiated a comprehensive 10-year *in vivo* study commencing in 1985. One of the primary motivations of this study was to assess the long-term effects, if any, of implantation on various suture materials. Ethicon selected PROLENE (polypropylene based), PVDF (polyvinylidene fluoride), ETHILON (nylon 6 and nylon 6,6), and Novafil (polybutester) monofilament 5-0 sutures to be examined in this study. Periodic evaluations were performed after two, five, and seven years *in vivo*, with baseline testing of unimplanted sutures also performed at each period. Each periodic evaluation consisted of generating mechanical and chemical property data as well as surface morphology micrographs to capture any physical changes in the candidate suture materials. In this study, twenty-four mature female Beagle dogs served as animal models (five animals per study period, plus four replacements in case of premature death). Each animal had sutures implanted in six different locations, and each implant location received a bundle of six sutures (with each bundle containing a single type of suture). A simplified schematic of the surgery sites is shown in Figure 9.

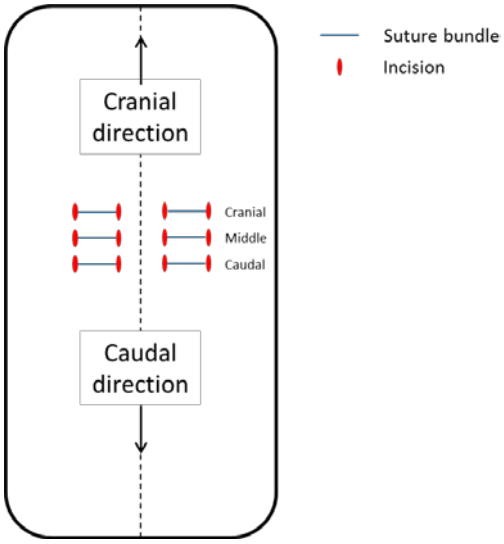

Figure 9. Simplified illustration of the ventral area of a dog torso, showing the location of the six suture implantation sites.

Five dogs were euthanized at each study period. For each suture type, one strand (selected at random) was immediately placed, without cleaning or being allowed to dry, into a test tube filled with sterilized deionized water to be examined and imaged with optical (OM), scanning electron (SEM), and infrared (IR) microscopy.

The remaining five strands were examined for surface damage, and then placed into saline-soaked towels in preparation for tensile testing, which was performed on the explanted strands of each suture type and ten non-implanted exemplars. After testing, the chemical groups present on the surfaces of the fragments were identified by FTIR, and the molecular weight was evaluated by inherent viscosity, and gel permeation chromatography (GPC).

Study Results

In this study, prior to additional testing and examination, FTIR spectra were taken on all explanted sutures to verify that they had been correctly identified during the explantation procedure.[100]

[100] Ethicon's Seven Year Dog Study (ETH.MESH.09888187) pg.115.

IR microscopy is a technique very similar to FTIR, albeit with smaller spatial resolution. This technique made it possible to compare the chemical groups present in cracked and non-cracked regions. After seven years *in vivo*, spectra for PROLENE sutures showed "a broadened weak absorbance at about 1650 cm^{-1}," Ethicon's scientists concluded that this was "possible evidence of slight oxidation."[100] The absorbance peak typically assigned to carbonyl containing functional groups in oxidized polypropylene is 1650–1810 cm^{-1}.[8,95,96] However, it is important to note that these samples were not cleaned, in fact tissue was still present on the surface of the suture and "cracking of the suture was seen through the tissue."[101] The existence of tissue, including tissue that may contain lipids or fatty acids, could readily account for the observed carbonyl functionality on the cracked surface of the suture; therefore, no scientific conclusions can be drawn by IR microscopy regarding the oxidation of PROLENE sutures. The spectra from cracked areas on ETHILON and Novafil sutures were not different than spectra obtained from uncracked areas. However, it was noted that absorbance frequencies related to oxidation "would be masked by the strong carbonyl absorbances normally observed for these sutures."[100] Thus, no conclusions could be drawn from the IR microscopy of any of the examined explanted sutures.

Direct molecular weight measurements via GPC were performed on both unimplanted controls and PROLENE sutures after seven years *in vivo* to determine if a shift in molecular weight had occurred. It is worth mentioning that direct measurements of molecular weight reduction are the most accurate and reliable method to assess degradation in polymeric materials. Results (shown in Table 1) indicated that "there was no significant difference in molecular weight between the 4-0 PROLENE control and the seven year explant."[100] The findings from this study are clear. Within the margins of statistical error, none of the implanted sutures suffered any meaningful losses in molecular weight and therefore, by definition, were not degraded.[102]

[101] Ethicon's Seven Year Dog Study (ETH.MESH.09888189) pg.117.
[102] This observation is also significant because it directly contradicts inferences by Plaintiff's experts that low molecular weight degradation materials from PROLENE are leaching into adjacent tissue.

Table 1. Molecular weight of exemplar PROLENE compared to explanted PROLENE sutures after 7 years *in vivo*.[84,103]

	M_w	M_n	PDI
Exemplar	324,000	60,000	5.4
Dog # 2007 site 1	322,000	69,000	4.7
Dog # 2007 site 6	323,000	63,000	5.1
Dog # 1995 site 3	327,000	59,000	5.5
Dog # 2019 site 3	331,000	64,000	5.2
Dog # 2019 site 2	332,000	57,000	5.8
Dog # 2008 site 2	322,000	53,000	6.1

Inherent viscosity tests of ETHILON and Novafil sutures were performed on samples from the seven year study period and compared to data from one and two year samples. The inherent viscosity of a polymer is directly related to its molecular weight. Obtained data showed no change in inherent viscosity in either type of suture after 1–2 years *in vivo* residence. However, after seven years the values ranged from 75% to 93% of those in the one and two year study period for the ETHILON sutures and 75% to 90% for the Novafil sutures.[104]

A polymer's mechanical properties are directly influenced by its molecular weight. When a polymer experiences chemical degradation, including oxidation, its polymer chains are cleaved and reductions in molecular weight are realized. From a bulk physical property standpoint, chemical degradation/molecular weight loss generally results in embrittlement of the material. Embrittlement is best described as a decrease in a material's elongation-at-break, ductility or toughness (area under the stress-strain curve) meaning that the material's ability to stretch, prior to fracturing, has been reduced (Figure 10). Quantifiable changes or shifts in a material's ductility due to degradation are easily computed by performing tensile tests on control and degraded specimens.

[103] The values in this table have been corrected to correct for typographical errors in previous reports.

[104] Ethicon's Seven Year Dog Study (ETH.MESH.09888188) pg.116.

In contrast, a polymer's ductility and toughness can increase as a result of plasticization. Plasticization of polymers is well documented in the scientific literature and occurs when low molecular weight compounds diffuse from an external source into the bulk polymer and physically change the intermolecular forces between polymer chains.[105] Specifically, plasticization of a polymer will result in a decreased modulus, increased elongation at break, and decreased breaking strength. Of equal importance is that plasticization is not a chemical degradation mechanism and does not, itself, result in a reduction in molecular weight.

[105] Wypych, G. *Handbook of Plasticizers*. Burlington: Elsevier Science, 2013.

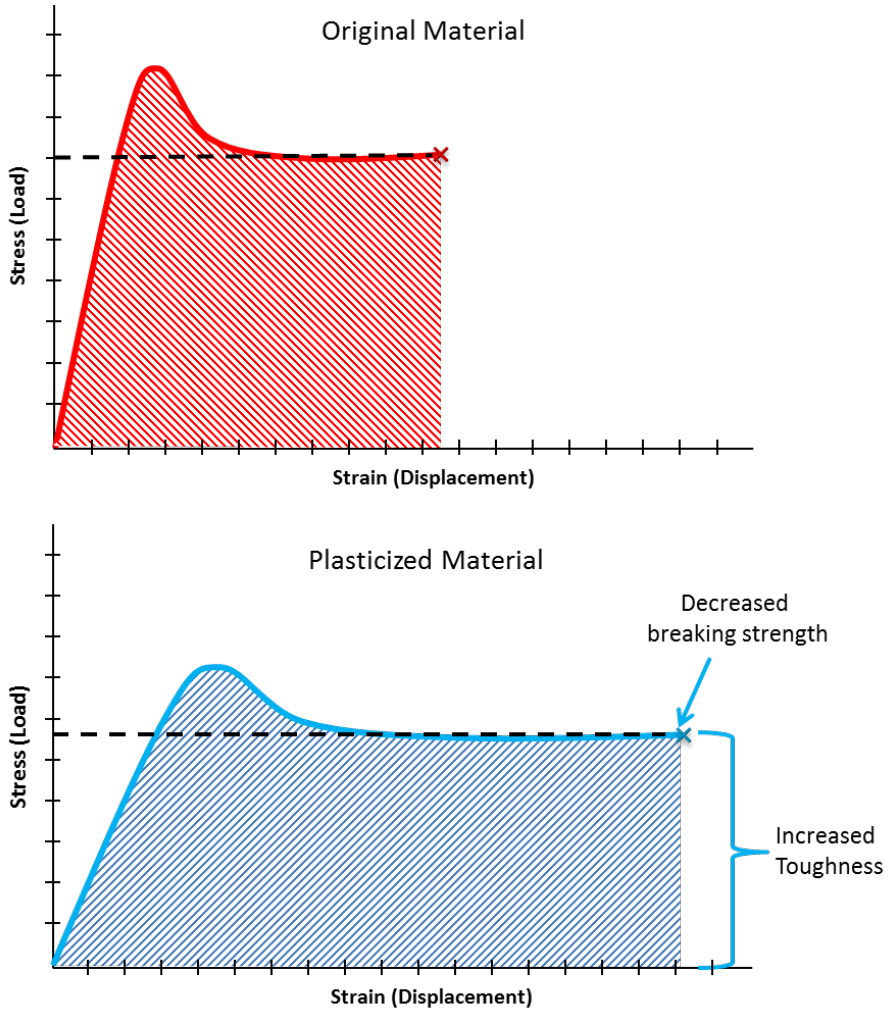

Figure 10. Schematic stress-strain curves for a non-plasticized and a plasticized material. Note the increase in toughness (area under the stress-strain curves) due to plasticization.

In addition to the molecular weight analysis, Ethicon evaluated the mechanical properties of explanted sutures from the seven year dog study to further determine if the bulk physical properties of the PROLENE material were being degraded during implantation. Tensile testing of sutures was performed on both pristine unimplanted and explanted sutures to evaluate the effect of implantation time on the mechanical properties of the suture material. The resulting breaking strength, elongation at break, and Young's modulus are summarized graphically in Figure 11. These tests revealed that ETHILON and Novafil sutures exhibited the greatest

decrease in breaking strength, with a 37% and 14% decrease respectively.[106] Furthermore, the physical appearance of the ETHILON sutures was reported as "fragile and worn out with spotted surface."[107] Conversely, "no significant change after seven year (sic) of implantation"[107] in breaking strength was reported for both PROLENE and PVDF sutures.

The elongation at break reported for all explanted suture types increased after seven years and can be seen in Figure 11. The most dramatic elongation *increase* was reported in PROLENE samples, which exhibited a 111% increase over pristine, non-implanted control samples.[106] A dramatic increase in ductility, in conjunction with a reduction in modulus (stiffness) is not indicative of degradation or oxidation, but instead confirms the PROLENE material's ductility and toughness *improve* as a function of implantation time and the improvement is most likely attributed to *in vivo* plasticization.

[106] Ethicon's Seven Year Dog Study (ETH.MESH.11336183) pg.155.

[107] Ethicon's Seven Year Dog Study (ETH.MESH.11336181) pg.153.

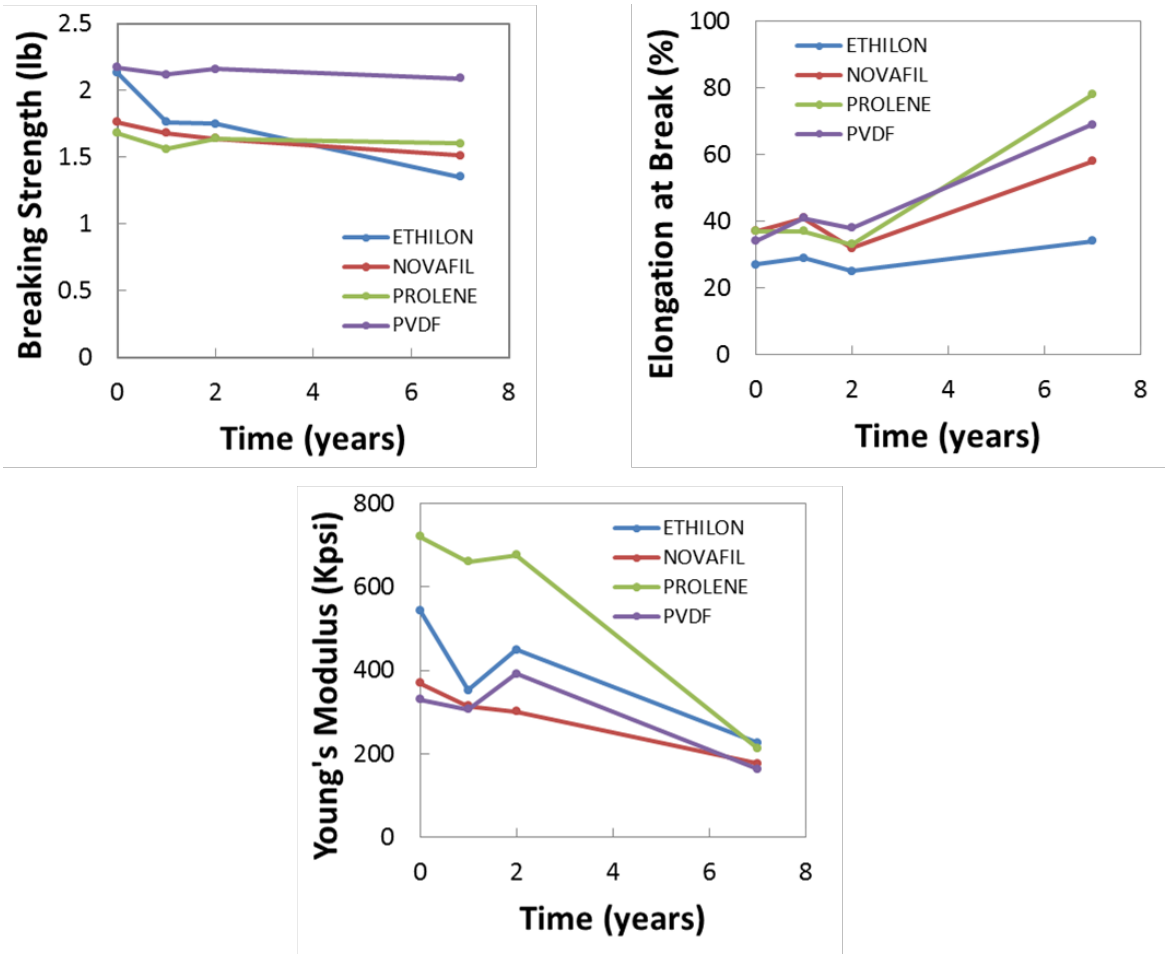

Figure 11. Summary of tensile tests performed on ETHILON, Novafil, PROLENE and PVDF sutures in Ethicon's Seven Year Dog Study.

Surface examinations of one suture of each type from each site were performed using both OM and SEM. Microcracking and/or damage was observed on the surface of the sutures as summarized in Table 2. Cracking was considered the most severe and widespread on ETHILON sutures, and was observed after one year *in vivo*. The presence of cracks on explanted Novafil sutures did not follow a clear trend, as seen in Table 2. After seven years *in vivo*, transverse cracking was not observed to a high degree on the Novafil sutures, although other signs of surface damage such as longitudinal scratches and a longitudinal crack were observed.[104] Transverse cracking was not observed on the surface of PROLENE sutures after one year *in vivo;* however, after seven years the appearance of cracking was reported on the surface of 50%

of the sutures. Throughout the seven year study, only one of the PVDF explanted sutures was reported to have "possible cracks" on the surface.[108]

Table 2. Summary of suture surface examinations. The number of sutures exhibiting damage (transverse cracking, longitudinal cracking, scratches, etc.) and the total number of sutures of each type after one, two, five and seven years *in vivo*.

	1 year[108]	**2 years**[108]	**5 years**[109]	**7 years**[110]
PROLENE	0 of 8	1 of 8	2* of 7	4 of 8
PVDF	0 of 8	1 of 8	0 of 7	1 of 7
ETHILON	7 of 7	5 of 7	8 of 8	8 of 8
NOVAFIL	4 of 7	2 of 7	0 of 8	4 of 7

* One additional suture revealed cracking only after drying.

Conclusion

Overall, Ethicon invested substantial resources in their multi-year investigation into the composition of the cracked outer layer observed on explanted PROLENE sutures. Ethicon's Seven Year Dog Study data strongly confirms that PROLENE does not experience any meaningful degradation *in vivo*. Rather, the material exhibits enhanced ductility and rupture resistance after long-term implantation.

[108] Ethicon's Seven Year Dog Study (ETH.MESH.11336081 – 11336082) pg.92-93.

[109] Ethicon's Seven Year Dog Study (ETH.MESH.11336165-11336168) pg.101-104.

[110] Ethicon's Seven Year Dog Study (ETH.MESH.09888191) pg.119.

Exponent's Analysis of Cleaned Explanted Mesh

To investigate Plaintiffs' allegation of *in vivo* oxidation of polypropylene, Exponent developed a robust and thorough cleaning procedure based on the work of Thames[86] to remove biological material from the surface of explanted meshes. As mentioned previously, the presence of residual biological material can confound analytical testing and lead to misguided interpretations of the resulting data.[111]

Biological material can be difficult to remove particularly after storage in formalin, a preservative solution which crosslinks proteins.[12,13,14] A study by de Tayrac[49] showed that the cracked crust layer which developed on the surface of polypropylene-based mesh implanted in Wistar rats was removed after a wash with dimethyl sulfoxide (DMSO) and ultrasonic shock treatment when the samples were not stored in formalin prior to cleaning, indicating that the crust was not associated with polypropylene degradation. While other studies claimed polypropylene degradation due to the observed cracked crust layer, these studies did not thoroughly clean the explanted samples prior to analysis, which likely resulted in confounded data.[111]

To evaluate the potential effects of implantation on PROLENE mesh, Exponent evaluated explants of various implantation times before and after thorough cleaning. Consistent with the procedure published in literature,[86] Exponent's cleaning experiments were performed through a series of successive immersions in distilled water, bleach and enzymatic solutions.[112] The cleaning process was intended to reverse formalin crosslinking, remove bulk tissue and other biological materials, and break down the absorbed proteins on the mesh surface. The as-received explants, as well as the exemplar (i.e., non-implanted),[113] and QUV oxidized[114] controls were

[111] See summaries of work performed by Clavé, Costello, Cozad, Mary, Wood, Talley, and Imel outlined earlier in this report.

[112] Complete details of this cleaning procedure and sample histories can be found in my Wave 4 report authored on Feb. 14, 2017, which I incorporate by reference.

[113] Exemplar PROLENE mesh included Prolift+M, Prolift, TVT, Gynemesh, and TVT Secur.

cleaned using the same procedure. The samples were visually examined, photo documented, weighed, and analyzed via optical microscopy and SEM at various steps in the cleaning procedure.[115] EDS was also performed on the samples after the first distilled water soak and first bleach treatment.[116] SEM and EDS were specifically utilized to examine the external crust material and the underlying PROLENE mesh.

Upon receipt, the samples were weighed, imaged using optical microscopy, and further divided (as needed) to facilitate analysis. The explants were initially covered in varying amounts of bulk tissue. Successive cleaning resulted in removal of bulk tissue, as confirmed visually and by optical microscopy, until the majority of the tissue was removed and the explants appeared nearly identical to their corresponding exemplar device (Figure 12).

Non-oxidized exemplar controls that underwent the same cleaning procedure as the explants showed no changes visually or by optical microscopy as the cleaning progressed (Figure 12D), indicating the cleaning procedure did not alter the PROLENE material.[117] Conversely, due to the brittle nature of the QUV oxidized controls, fiber fracture was observed during the cleaning process (Figure 12E). No such fracture was observed in any of the explants during the cleaning process.

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[114] To induce oxidation, TVT PROLENE mesh was placed inside a Q-Lab QUV Accelerated Weathering Tester and irradiated with 0.98 (W/m^2) UV light at 60^{o}C for approximately 6 days.

[115] QUV oxidized PROLENE mesh was analyzed via SEM after an initial water soak, after the first exposure to bleach, and at the conclusion of the cleaning process.

[116] Exemplar and QUV oxidized PROLENE mesh was analyzed by EDS after the first bleach treatment.

[117] The multifilament Prolift + M exemplar requires special mention. As expected, the resorbable polyglecaprone material was fully dissolved during the bleach treatments, while the PROLENE material did not change.

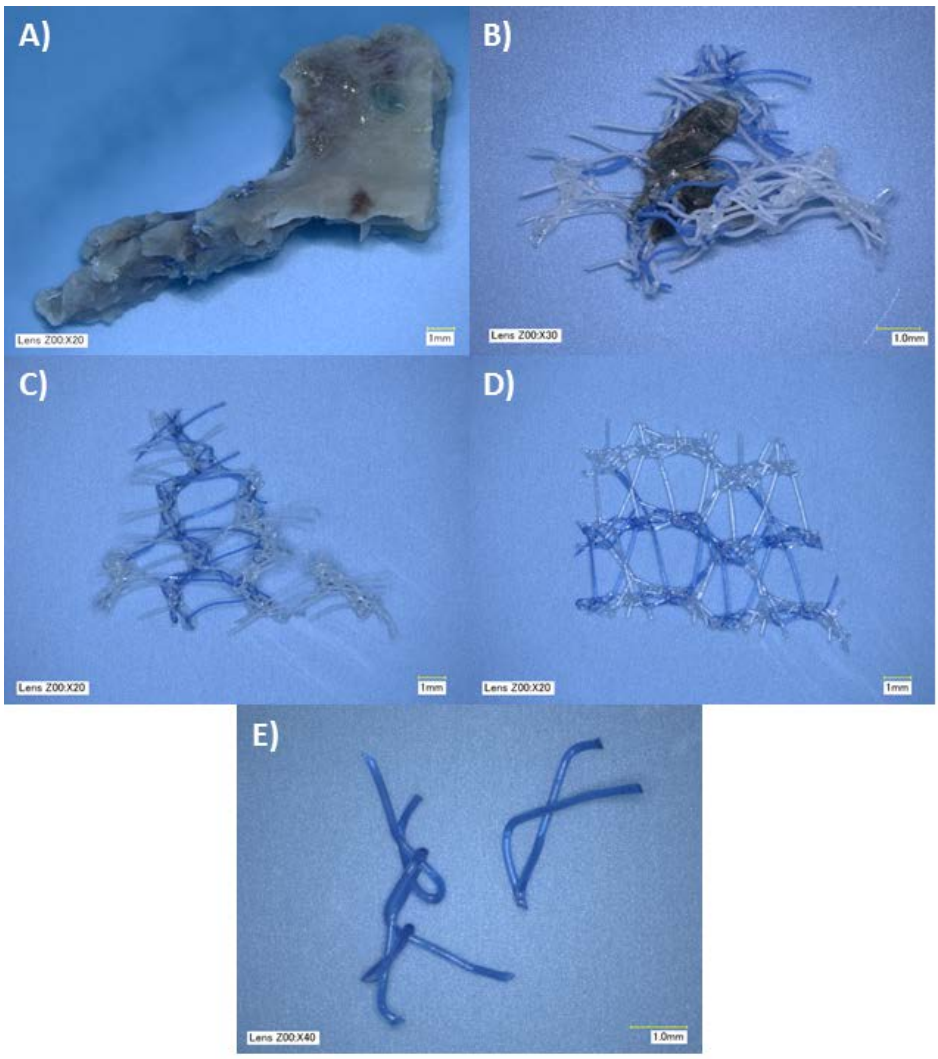

Figure 12. Optical microscopy images of a representative explant showing progressive removal of tissue. A) Covered in tissue before cleaning, B) after the first NaOCl treatment, and C) after the final NaOCl treatment. D) Gynemesh exemplar after the final NaOCl treatment, and E) a QUV oxidized TVT control after the final NaOCl treatment.[112]

SEM images of the progressively cleaned explanted meshes confirmed the same trends observed in optical microscopy. Initially, the explants were covered by bulk tissue and a cracked layer of material, often described by others in literature as oxidized polypropylene.[49,50,53,58] However, as cleaning progressed, the cracked layer was gradually removed, exposing fibers with extrusion

lines similar to those of the exemplar meshes (Figure 13).[118] Extrusion lines[119] are expected on the surface of fibers,[120] but would not be present in the bulk of the fiber if the top layer was oxidized and stripped away during cleaning.

[118] When possible, all SEM images were taken in identical locations to provide direct comparisons of each successive cleaning step.

[119] Gooch, J., *Encyclopedic Dictionary of Polymers, 2nd ed.* Springer Science & Buisiness Media, 2010, pg. 214.

[120] Koopmans, R., Den Doelder, J., Molenaar, J., *Polymer Melt Fracture*. CRC Press, 2010, pg. 93.

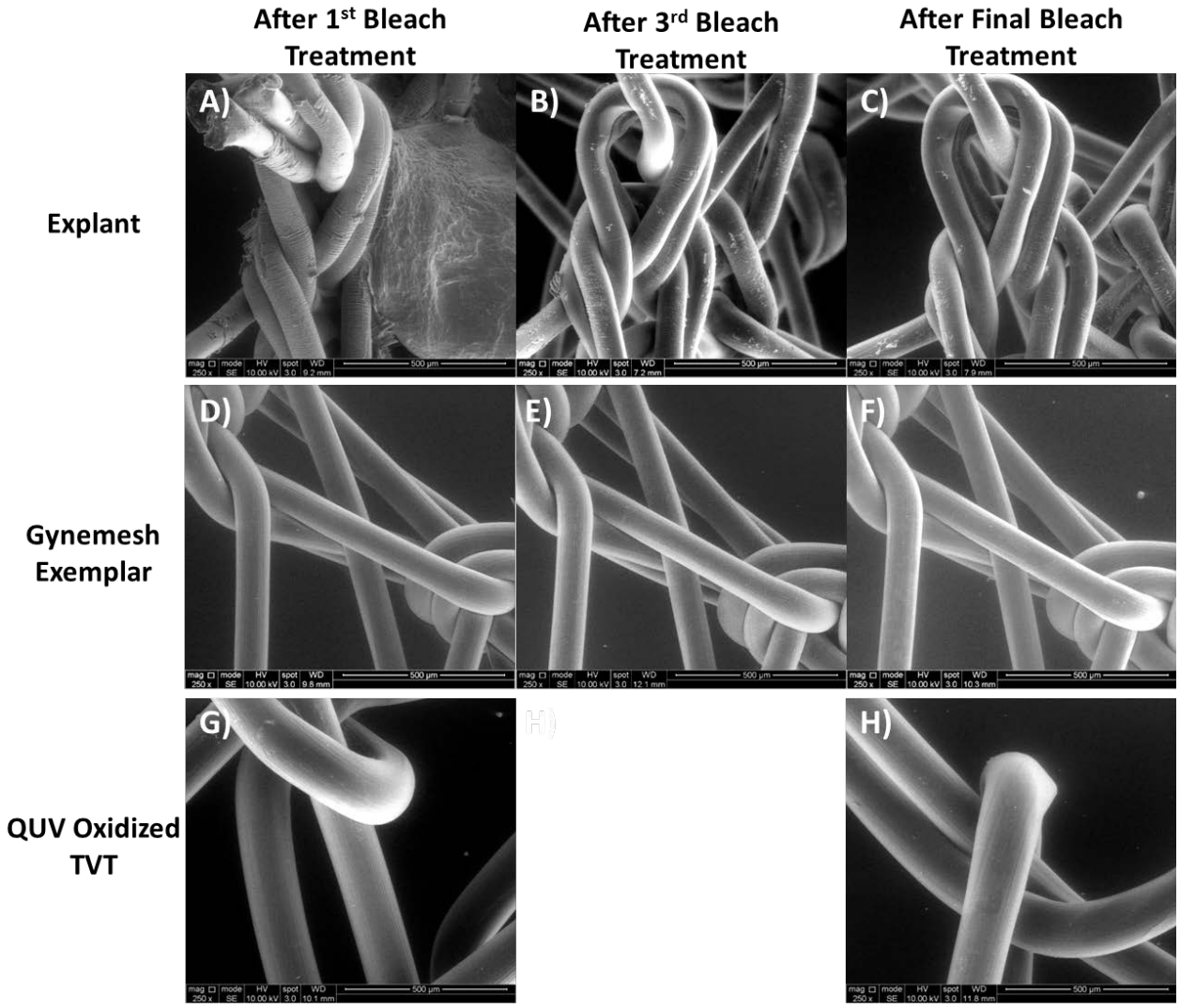

Figure 13. SEM images of a representative Gynemesh explant (first row), a Gynemesh exemplar control (second row), and a QUV oxidized TVT exemplar control (third row) at various stages during the cleaning process. Images shown were taken after the first bleach treatment (A, D, G), after the third bleach treatment (B, E), and after the final bleach treatment (C, F, H). All images at 250x. Note: G) and H) not at identical locations.[112]

An investigation of the elements present both on the explanted PROLENE fibers, and in the cracked outer surface coating of an explanted mesh was conducted by EDS analysis. EDS mapping was performed after the initial water soak and after the first bleach treatment (Figure 14). As expected, the bulk tissue covering the explant is composed predominantly of carbon with detectable amounts of other elements commonly found in biological materials (e.g., nitrogen, oxygen, sodium, phosphorous, sulfur, and calcium).[73] Throughout the progressive cleaning steps, the explants and the associated cracked outer layer showed that carbon remained as the predominant element, though other common biological elements were also detected. Notably, as bulk tissue is known to be composed of proteins (rich in nitrogen), the EDS semi-quantitative analysis detected a 5% concentration of nitrogen in the area analyzed. The low detection rate is expected as nitrogen and other light elements have low fluorescent yield, making it difficult to accurately quantify and detect using EDS.[121,122] After the initial water soak, the cracked layer observed on the surface of the explanted polypropylene fibers exhibited elements associated with biological matter, including nitrogen, phosphorus, sodium, sulfur, and calcium (Figure 14B). After cleaning with bleach and removing a portion of the outer cracked layer, nitrogen was no longer detected due to its low detection limit and the reduced amount of biological material present after the first tissue removal step (Figure 14C). However, while absent in the non-cracked regions, other biological elements such as phosphorus, sodium, chlorine, sulfur, and calcium were clearly identified in the localized cracked outer surface layer, thereby confirming the cracked crust layer is derived from biological material and not oxidized polypropylene. As a control, an EDS map was also collected on a QUV oxidized exemplar after the first bleach treatment and found no phosphorus, sodium, chlorine, sulfur, or calcium, confirming that detection of these elements was not due to PROLENE oxidation or the cleaning process (Figure 14D).

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[121] Goodhew, P., Humphreys, J., Beanland, R., *Electron Microscopy and Analysis, 3rd edition*. London, UK: Taylor and Francis, 2001.

[122] Australian Microscopy & Microanalysis Research Facility Training for Advanced Research. Available at www.ammrf.org.au/myscope/analysis/eds/xrayintensity/. Accessed on 2-2-17.

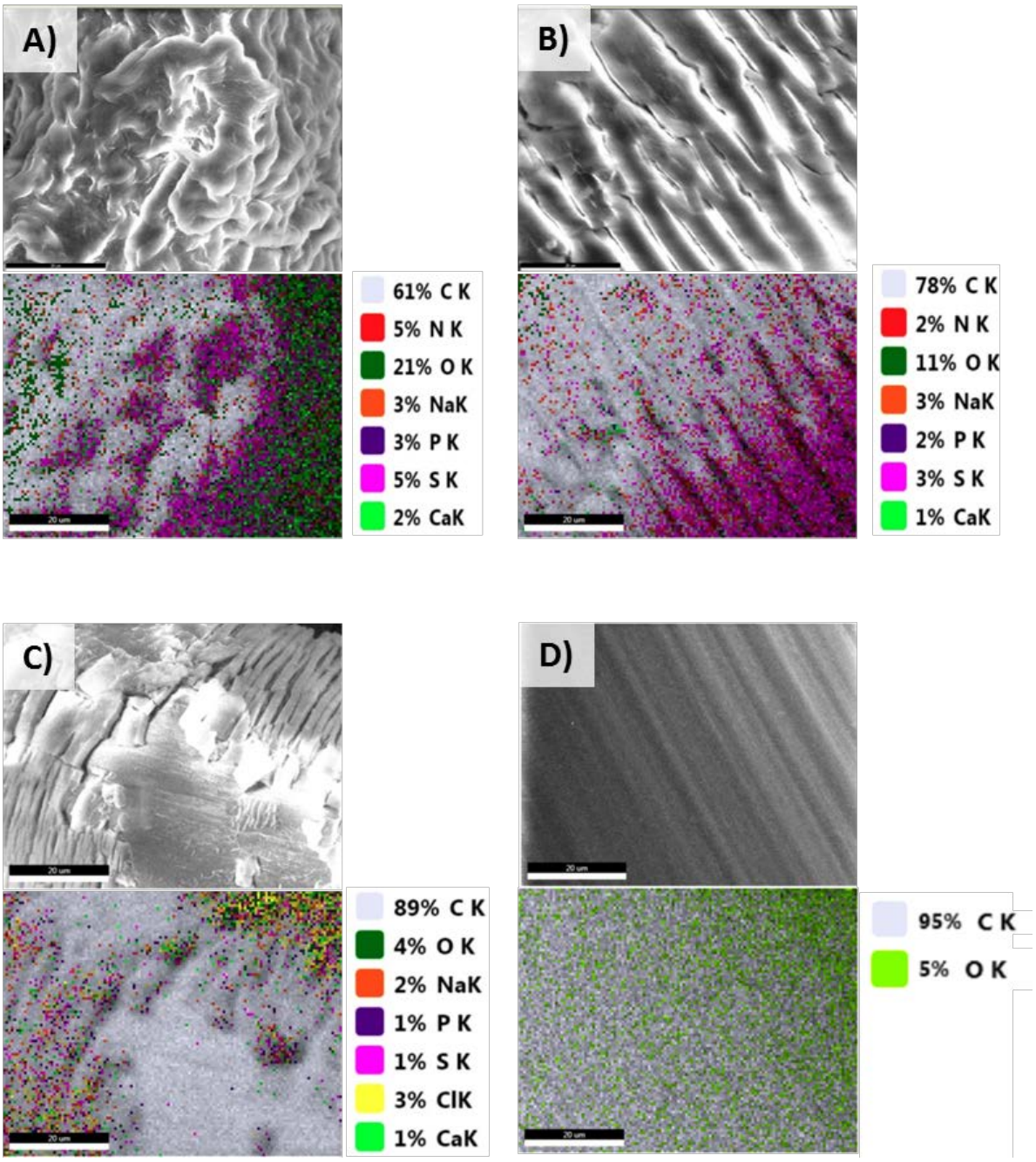

Figure 14. SEM images and EDS elemental analysis of a representative explant (A, B and C). Images and spectra were acquired after the initial water soak on bulk tissue covering the explant (A), as well as on the cracked outer layer covering the mesh fibers (B) and after the first bleach treatment after the cracked outer layer had been partially removed from the underlying fiber (C). SEM and EDS analysis were also performed on an intentionally QUV oxidized TVT control sample after the first bleach treatment (D).[112]

Artifacts in Microtome Processing

Microtoming is a known method of preparing thin cross sections of both biologic and synthetic materials.[123] The process of microtoming involves preparing a sample by embedding in paraffin or another stiff matrix, then making slices of varying thickness with a very sharp knife or blade. This process, which has been used in polymer science for decades, is often used for the purpose of preparing very thin slices of cross sections as part of a staining protocol in pathology applications to illuminate different types of cells and/or tissue that may be present within a sample.

It is important to note that not every material can be prepared by microtoming. Often, samples that are too soft cannot be sectioned effectively, resulting in a poorly prepared material slice with extraneous artifacts, including edge imperfections, which are not representative of the pre-sectioned material sample. To avoid these artifacts, biological tissue samples are often fixed, which among other effects, hardens the tissue for microtoming.[12]

Likewise, heterogeneous samples with both hard and soft matter can be difficult to microtome without inducing artifacts. As an example, McInnes reports on artifacts caused by bone fragments in soft brain tissue. The hard fragments can be "moved by the microtome knife-edge during cutting and this causes shattering and distortion of the tissue section."[124]

During the cutting process, if the microtome knife is set at too acute of an angle or if the knife is too dull, it can compress the tissue specimen as it is being cut. This effect is exacerbated when a particularly soft material is being sectioned. In this case, the microtome knife can compress the tissue specimens and result in streaks, cracks, waviness, and other artifacts that run parallel to

[123] Bell, G. R. "Microtoming: An Emerging Tool for Analyzing Polymer Structures." *Plastics Engineering*.
[124] McInnes, E. "Artefacts in Histopathology." *Comp. Clin. Pathol.*, (2005) 13(3):100–108.

the edge of the microtome knife, and in some cases, rendering the sectioned tissue specimen unable to be adequately processed via microscope examination.[124,125]

[125] Janzen, W., Ehrenstein, G. W. "Microtomy of Polymeric Materials Part 2: Application of Microtomy." *Pract. Metallogr.*, (1989): 26549–558.

Exponent Investigation into Staining of Intentionally Oxidized PROLENE Mesh

Introduction

Plaintiff's expert, Dr. Vladimir Iakovlev, opines that Ethicon's PROLENE mesh degrades *in vivo* based on a cracked layer observed on the outer surface of mesh fibers after explantation.[126] While this assertion has been made by other plaintiffs' experts,[127,128] Dr. Iakovlev claims that the outer degradation layer is oxidized and "differs from the non-degraded core by its ability to trap histological dyes in the nanocavities produced in polypropylene due to degradation."[129] Dr. Iakovlev bases his conclusions on flawed experiments in which he purports to show that oxidized, degraded PROLENE is stained using histological dyes such as Hematoxylin and Eosin (H&E), yet fails to perform control experiments to confirm this theory. The purpose of the following experements is to address the scientific deficiencies of Dr. Iakovlev's experiments and conclusions from a polymer science perspective. This work does not attempt address issues related to histology[130] or Dr. Iakovlev's histological analysis.

Hematoxylin and Eosin (H&E) Stain

Hematoxylin and Eosin, also referred to as H&E, is a common stain used for illuminating components of cells and tissue, many of which are long molecules (polymers). The hematoxylin dye solution itself is a mixture of hematoxylin, hematein, aluminum ions, and solvent. It is used in combination with a "mordant" compound that helps link it to the tissue. This mordant is typically a metal cation, such as aluminum. The complex is cationic (positively charged) and

[126] Expert report of Dr. Iakovlev dated 5-23-15, p. 54.

[127] Expert report of Dr. Howard Jordi dated 8-24-15, p. 13.

[128] Expert report of Dr. Scott Guelcher dated 8-24-15, p. 2.

[129] Expert report of Dr. Vladimir Iakovlev dated January 29, 2016, p. 18.

[130] Histology relates to the microscopic study of tissue. Here within, I focus on the microscopic study of PROLENE polymer fibers, although the chemistry of histological staining is discussed from a background perspective.

can react with negatively charged basophilic cell components, such as nucleic acids in the nucleus, rough endoplasmic reticulum, ribosomes, and acidic mucin. Eosin, used in combination with Hematoxylin, is negatively charged and attracts positively charged molecules. It stains structures with positive charges, e.g. cellular membranes, cytoplasm, connective tissue, and extracellular matrix tissue.[131,132]

Ionic bonding is the most important type of bonding that occurs during histological staining.[131] The mechanism for H&E "staining" of tissue is simple ionic bonding between two charges: charge on the H&E staining molecules and charges on the molecules that comprise the tissue. As an example, amino acids are the molecular building blocks of proteins (which are also polymeric) and some of these amino acids contain a net charge as shown in Figure 15.[133] These charged compounds will bind ionically[134] (charge-to-charge) with H&E and appear stained. The H&E staining mechanism is not physical in nature. In other words, physical voids, cracks, or crevices in PROLENE (as posited by Dr. Iakovlev)[135] or other materials do not "trap" or hold H&E stain, especially after washing and rinsing, which is part of the accepted staining protocols.

Polypropylene or PROLENE molecules are not ionically charged and are therefore not expected to stain with H&E. Furthermore, as shown previously, oxidized polypropylene does not possess a distinct ionically charged region. Therefore, in accordance with not only first principles of polymer science, but also the accepted methodology and assessment routinely reported in the literature, oxidized polypropylene is not expected to be stained by H&E.

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[131] Veuthey, T. Dyes and Stains: From Molecular Structure to Histological Application. *Front. Biosci.*, (2014) 19(1):91.

[132] Education Guide: Special Stains and H&E Second Edition, Editors: George L. Kumar and John A. Kiernan., 2010 Dako North America, Carpinteria, California.

[133] Nelson D. L. and Cox M. M. *Lehninger Principles of Biochemistry*. Worth Publishers, 2000, p. 118–119.

[134] A common, familiar ionically bonded material is sodium chloride, or table salt, in which Na^+ and Cl^- are bound together by ionic attraction.

[135] Expert report of Dr. Vladimir Iakovlev dated January 29, 2016, p. 18, 92, 93.

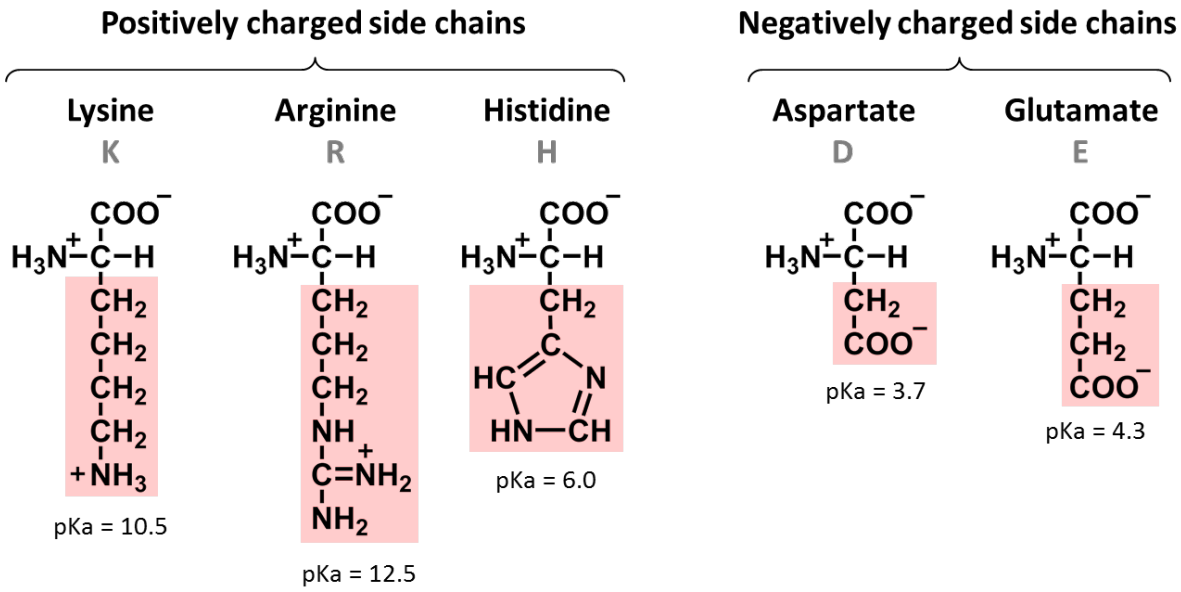

Figure 15. Amino acids that contain a positively or negatively charged side chain, resulting in net positive or negative charge, respectively.[133]

Experimental Investigation of the Capacity of PROLENE and Oxidized PROLENE to Accept H&E Stain

In addition to my reliance on the literature and first principles of polymer science, and to further validate my assertion that H&E is not expected to stain PROLENE or oxidized PROLENE, Exponent conducted a set of laboratory experiments that serve as the control experiments Dr. Iakovlev failed to perform in his expert report. The details of these experiments are provided below.

Sample Preparation Prior to Sectioning

Exemplar PROLENE Mesh

Pristine PROLENE mesh (Ref. No. 810041B, Lot No. 3661669) was received and kept in its original packaging until use. A clean razor blade was used to cut sections for laboratory analysis.

Chemically Oxidized PROLENE Mesh

Six sections of PROLENE mesh (Ref. No. 810041B, Lot No. 3661669) were oxidized according to the protocol published by Guelcher and Dunn.[63] Samples were incubated at 37°C for up to 5 weeks in oxidative media composed of 0.1 M $CoCl_2$ in 20 wt% H_2O_2. This solution purportedly simulates the oxidative microenvironment created by macrophages in response to a foreign object.[63] The oxidative solution was changed every 2–3 days. Prior to processing, the samples were copiously rinsed in de-ionized water, air-dried, and assessed for morphological changes using scanning electron microscopy (SEM).

QUV Oxidized PROLENE Mesh

Six sections of PROLENE mesh (Ref. No. 810041B, Lot No. 3661669) were placed inside a Q-Lab QUV Accelerated Weathering Tester and irradiated with 0.98 $(\frac{W}{m^2})$ UV-A and UV-B at 60°C for 5 days. As with the chemically oxidized meshes, the samples were assessed for morphological changes using SEM prior to processing.

Sample Mounting and Sectioning

Exemplar and oxidized mesh samples were embedded in both paraffin and resin (Technovit 7200), sectioned, and stained with Hematoxylin & Eosin. All processing was performed by an independent histology lab and observed by Exponent. Detailed embedding and staining protocols can be found in Appendix A.

Paraffin-embedded samples were prepared by following the protocol submitted by Dr. Iakovlev. Samples were sequentially dehydrated in reagent alcohol and Xylene substitute using an automated tissue processor, then embedded in Leica EM400 Paraffin wax. Sections of the paraffin blocks (4–6 μm thick) were obtained using a microtome, briefly floated in a 40–45°C water bath, then mounted onto slides. Sections were air-dried for 30 minutes then baked in a 45–50°C oven overnight.

Resin-embedded samples were sequentially dehydrated in reagent alcohol using an automated tissue processor, then embedded in Technovit 7200. The polymerized resin block was trimmed, cut, and ground to a thickness of approximately 50 µm.

Paraffin and resin-embedded samples were stained with Aqueous Eosin and Harris Hematoxylin using an automated stainer. All slides were imaged by Exponent personnel using a microscope equipped with polarizing filters.

Results

SEM on Oxidized Meshes

When viewed under SEM, the QUV-oxidized mesh exhibited external cracking (Figure 16), while the chemically-oxidized mesh did not (Figure 17). This differs from the results published by Guelcher and Dunn, who reported “pitting” and “flaking” in polypropylene meshes subjected to the same treatment conditions.[63]

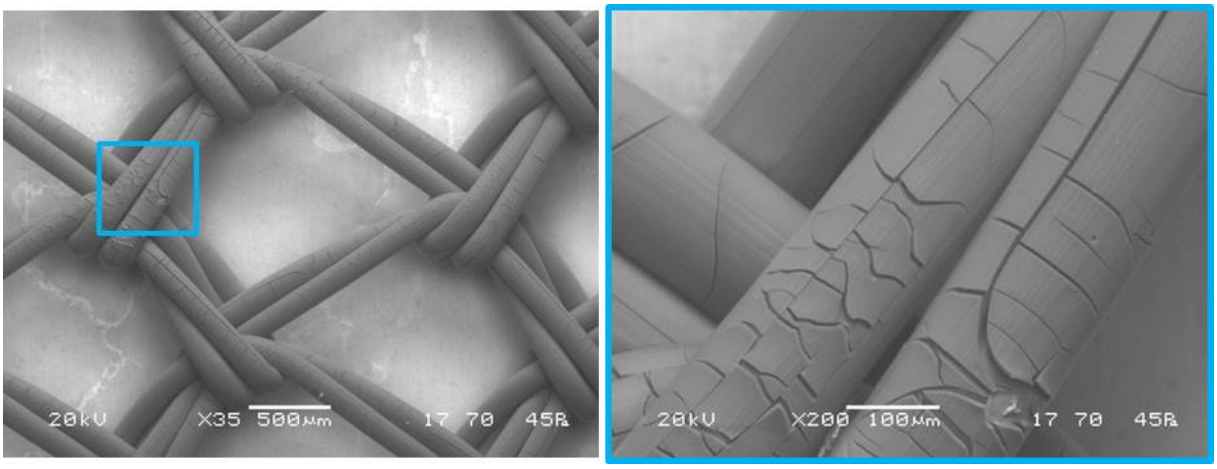

Figure 16. Scanning Electron Microscope images of QUV oxidized mesh.

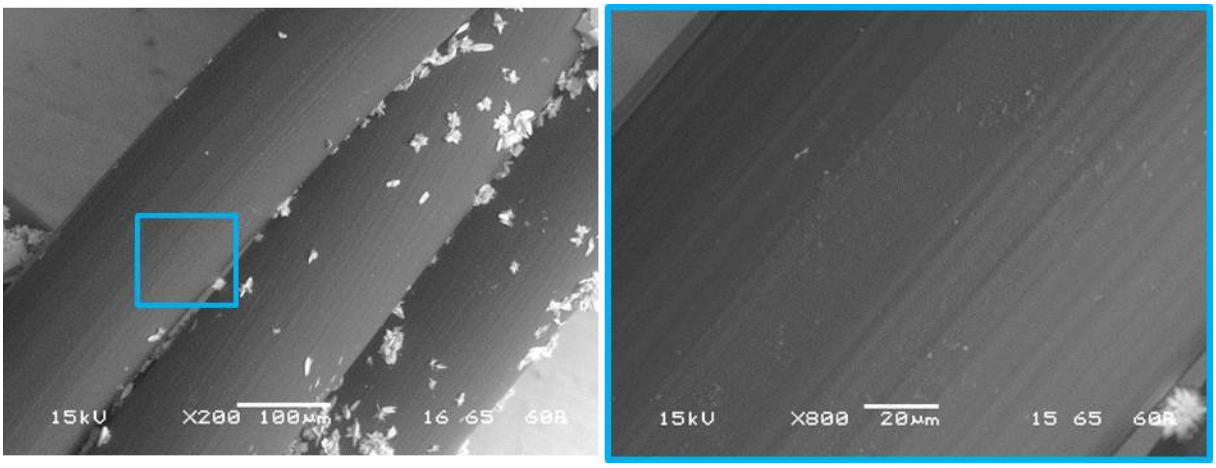

Figure 17. Scanning Electron Microscope images of mesh that was chemically-oxidized according to the Guelcher protocol.

Analysis and Experimental Validation

Six separate samples were simultaneously subjected to QUV irradiation; each contained approximately 120 individual fiber segments. While only one of these samples (Sample #2) was processed for H&E staining, it is reasonable to infer, based on SEM images of QUV-exposed samples, that a majority of the individual fibers in the treated samples were degraded and cracked prior to being subjected to the staining process. An SEM image of Sample #4 with enumerated fiber segments used as the basis for quantifying the cracked fibers is shown below in Figure 18.

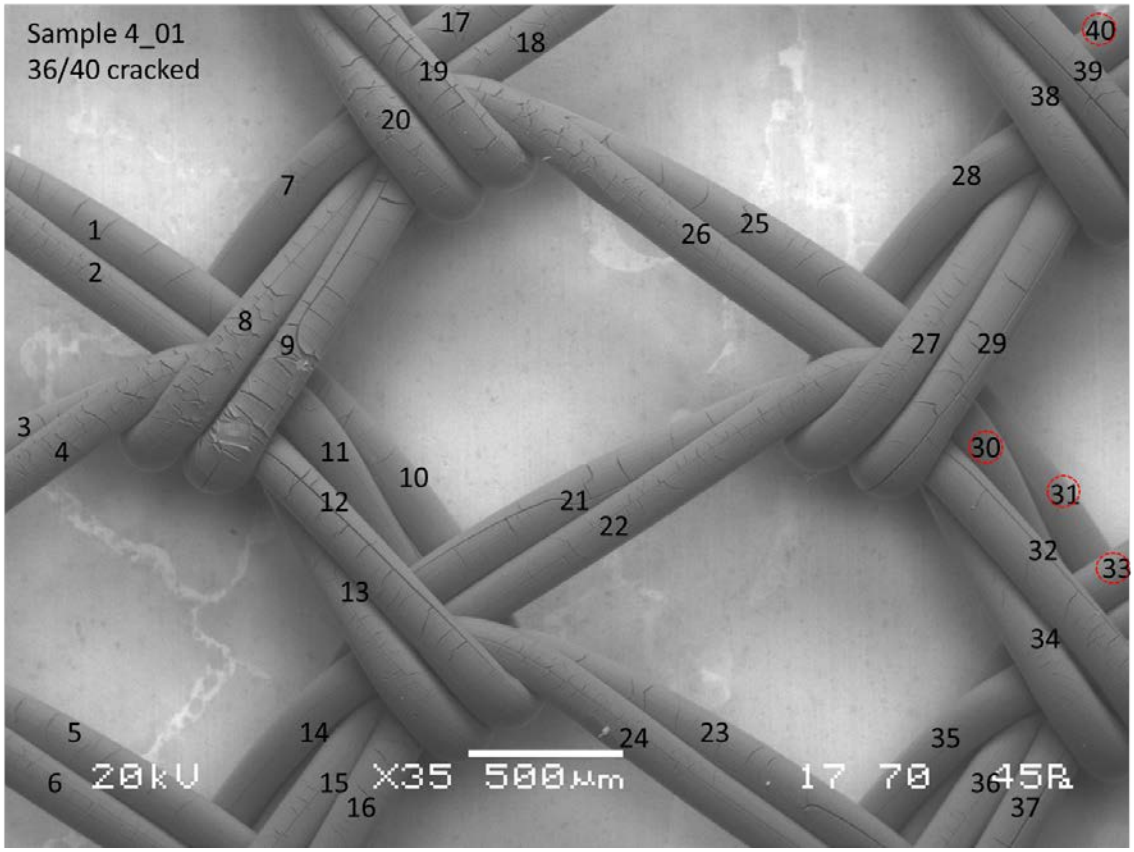

Figure 18. Scanning Electron Microscope image of QUV oxidized mesh. Numbered markings indicate individual fiber segments.

Each SEM image covers approximately one-third of the sample that was cut from the PROLENE device. The table below summarizes the findings of cracked fiber segments from portions of the three QUV-irradiated samples examined in the SEM (Samples #4, #5, and #6).

Table 3. Summary of Scanning Electron Microscope findings on QUV oxidized mesh.

Sample Number	Cracked Fiber Segments in SEM Image	Total Fiber Segments in SEM Image	% of Fiber Segments Cracked in SEM Image	95% Lower Bound on % of Cracked Fiber Segments in Sample
4	36	40	90%	80%
5	27	42	64%	52%
6	29	37	78%	66%

The rightmost column of the table presents the 95% lower confidence bound on the percentage of cracked fibers in the total sample. Although the observed percentage of cracked fiber segments varies for each of the three samples, the respective SEM images support a reliable statistical inference that, with 95% confidence, greater than half of the individual fibers in the entire sample will be cracked.

A simple conservative calculation shows that it is implausible that Sample #2 exposed to UV light and treated with histological dye contained no cracked fiber segments. Given that the treated sample contained approximately 120 fiber segments, each of which independently has a 50% probability of being cracked, the chance that none of the 120 fiber segments were cracked is only 1 in 2^{120}, or less than 1 in 10^{36} (1 followed by 36 zeroes). In other words, the probability that none of the fiber segments in Sample #2 were cracked at the time of staining is so infinitesimally small it renders the outcome, for all practical purposes, impossible.

Intentionally Oxidized PROLENE Meshes Were Not Stained by the Hematoxylin & Eosin Dyes

Positive Control – Rabbit Skin

A positive control (rabbit skin tissue) was included with the mesh samples and processed simultaneously in the automated tissue stainer to demonstrate the effectiveness of the protocol. PROLENE meshes were subjected to the staining protocol in the same batch.

The appearance of stain is evident when tissue is present and stain has been applied. Figure 19 shows the stark contrast between rabbit tissue that has not been treated with stain (left) and rabbit tissue that has been treated with stain (right). This experiment demonstrates that our protocol is effective in staining proteinaceous materials.

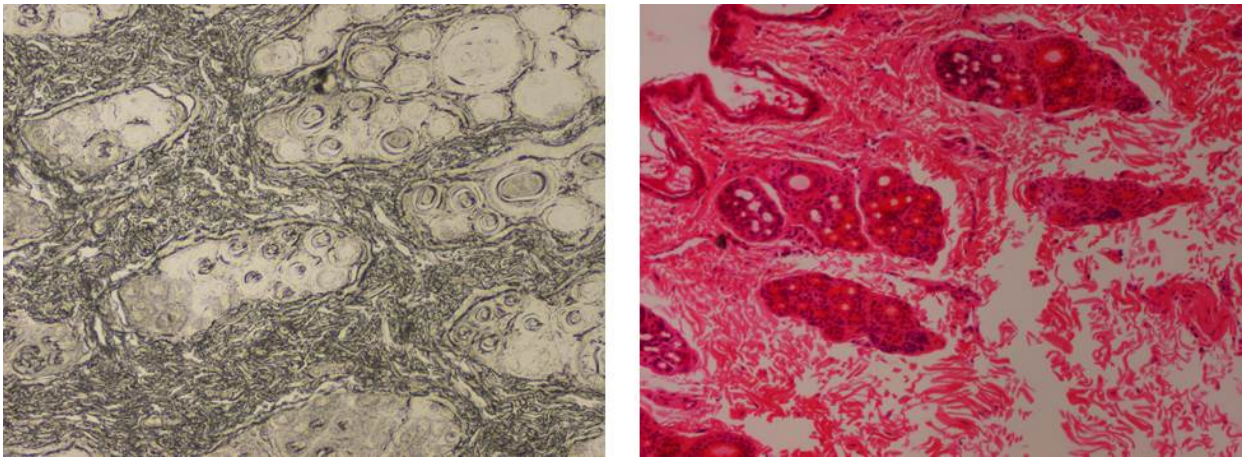

Figure 19. Processed and sectioned rabbit skin tissue not stained (left) and tissue that has been stained (right) are shown.

Non-Oxidized Control – Out-of-the-Box PROLENE Mesh

Exemplar PROLENE mesh samples with no prior exposure to laboratory UV or chemical oxidation were subjected to the Iakovlev staining protocol. As expected, the H&E stain did not bond to the PROLENE as displayed in Figure 20, confirming that the staining protocol is not effective in staining non-proteinaceous or non-ionic materials.

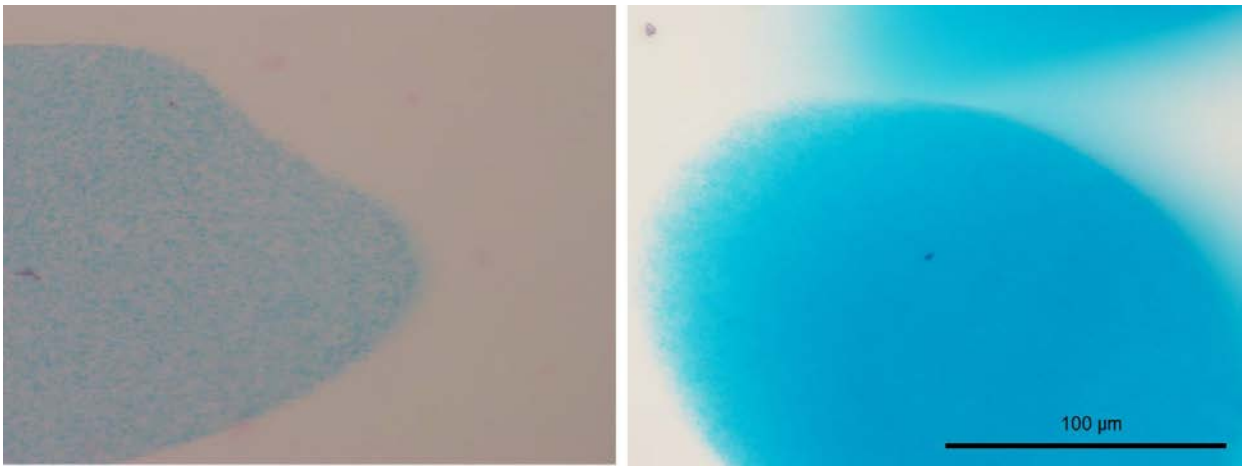

Figure 20. Pristine (exemplar) mesh embedded in paraffin (left) and resin (right), stained with H&E.

Intentionally Oxidized PROLENE – Chemical Oxidation

Exemplar PROLENE mesh samples exposed to the Guelcher chemical oxidation procedure were also subjected to the Iakovlev staining protocol. In total, twenty-two individual cross sections were examined. As shown in Figure 21, Figure 22, and Figure 23, the chemically oxidized PROLENE did not accept the H&E stain, thereby confirming the flawed methodology of Dr. Iakovlev.

Figure 21. Chemically oxidized PROLENE mesh embedded in paraffin (left) and resin (right), stained with H&E.

An additional observation made during these experiments was that manipulation of the microscope polarizers could create a “bark-like” appearance on the fiber exterior (Figure 22 and Figure 23). This effect is likely an artifact of the sectioning process caused by the varying thickness of the fiber across its diameter. Interestingly, what Dr. Iakovlev describes as PROLENE dye particles can be seen in the false “bark.”

Figure 22. PROLENE mesh chemically oxidized with the Guelcher protocol, embedded in resin, and subjected to the H&E staining protocol. Non-polarized light (left), plane-polarized light (center), cross-polarized light (right). No staining is evident.

Figure 23. PROLENE mesh chemically oxidized with the Guelcher protocol, embedded in resin, and subjected to the H&E staining protocol. Non-polarized light (left), plane-polarized light (right). No staining is evident.

Intentionally Oxidized PROLENE – UV Oxidation

Exemplar PROLENE mesh samples exposed to QUV oxidation were also subjected to the Iakovlev staining protocol. In total, over one hundred individual cross sections were examined. As shown in Figure 24, the QUV oxidized PROLENE did not accept the H&E stain. In addition, as shown in Figure 25, despite the fact that the fiber was cracked, and according to Dr. Iakovlev should have physically trapped stain, the QUV oxidized PROLENE did not accept the H&E stain, thereby again confirming Dr. Iakovlev's flawed methodology. Despite multiple

observations using high and low magnifications, polarized and non-polarized light, no evidence of the stain being trapped, captured, or otherwise bound within the cracks of the damaged mesh was observed.

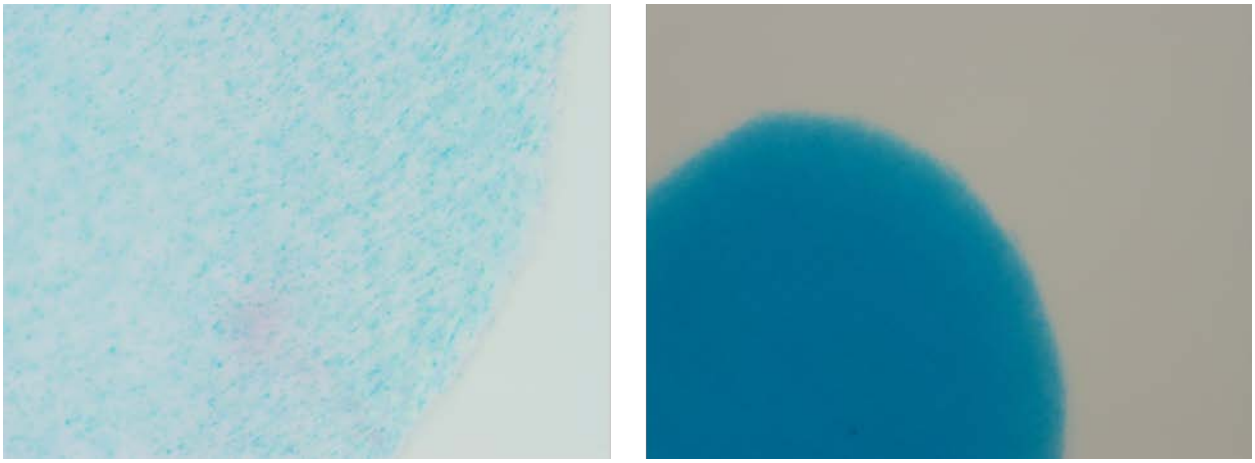

Figure 24. QUV-oxidized PROLENE mesh embedded in paraffin (left) and resin (right), stained with H&E.

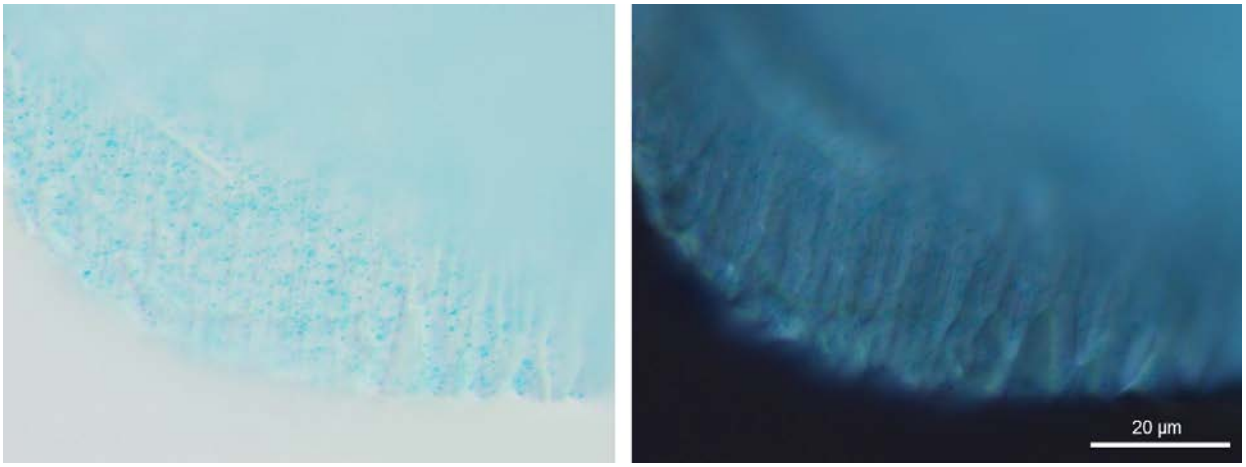

Figure 25. QUV-treated mesh exhibiting several cracks but no evidence of H&E stain. Image on the left was acquired in absence of polarization, the image on the right was taken with polarization.

Statistical Significance

A statistical analysis of my control experiment was scientifically unnecessary. In the microscopy experiments conducted, intentionally oxidized PROLENE was shown to not hold stain. No variability was observed in these results, meaning none of the nearly 150 individual fiber segment cross sections prepared and examined according to Dr. Iakovlev's staining protocol were found to have stained. The lack of variability in the experimental data supports the conclusion that these observations are essentially deterministic in nature, reproducible exactly or with negligible variability. As defined in *A Dictionary of Computing*, published by the Oxford University Press,[136] statistical methods are:

> "Methods of collecting, summarizing, analyzing, and interpreting variable numerical data. Statistical methods can be contrasted with deterministic methods, which are appropriate where observations are exactly reproducible or are assumed to be so."

In view of this definition, which distinguishes statistical from deterministic methods, the omission of a formal analysis—i.e., an application of statistical methods to the unvarying data in this experiment—is appropriate and consistent with generally accepted scientific practice.

Validation of Microscopy Experiments

To confirm the reliability of the methods and results of its microscopy experiments, Exponent repeated and expanded its work using three additional PROLENE TVT mesh devices, a PROLENE hernia mesh, PROLENE sutures, and commercially available polypropylene (not PROLENE) pellets . In addition to the examination of pristine (exemplar), and intentionally oxidized (QUV and chemical) polypropylene-based samples, sections of these PROLENE devices were coated in fetal bovine serum (a protein-rich medium) as a positive control. Further details of these experiments and corresponding results are included in Appendix H of this report.

[136] *A Dictionary of Computing*, Oxford University Press, 2004.

Imaging Artifacts

Microtome slicing of polymeric samples has been used in the field of polymer science for decades, and is a technique with which I am familiar.[137,138,139] Observation of thin-sliced polymeric specimens, including those that have been dyed, requires an understanding of potential artifacts that can exist as a result of the cutting and imaging process.

In some instances during this study, select images appeared to have a pink background when viewed on two separate computer monitors. An example of this is shown in Figure 26. The image on the left is the actual image file. The image on the right is a photograph of the same image file being displayed on a different monitor. A photograph was taken to capture the color difference. This perceived change in hue is one example of how optics, lighting, and related artifacts may influence visual observations.

[137] Wang, X., Zhou, W. Glass Transition of Microtome-Sliced Thin Films. *Macromolecules*, (2002) 35(18):6747–6750.

[138] Stiftinger, M., Buchberger, W., Klampfl, C. W. Miniaturised Method for the Quantitation of Stabilisers in Microtome Cuts of Polymer Materials by HPLC with UV, MS or MS2 Detection. *Anal. Bioanal. Chem.*, (2013) 405(10):3177–3184.

[139] Janeschitz-Kriegl, H., Krobath, G., Roth, W., Schausberger, A. On the Kinetics of Polymer Crystallization under Shear. *Eur. Polym. J.*, (1983) 19(10-11):893–898.

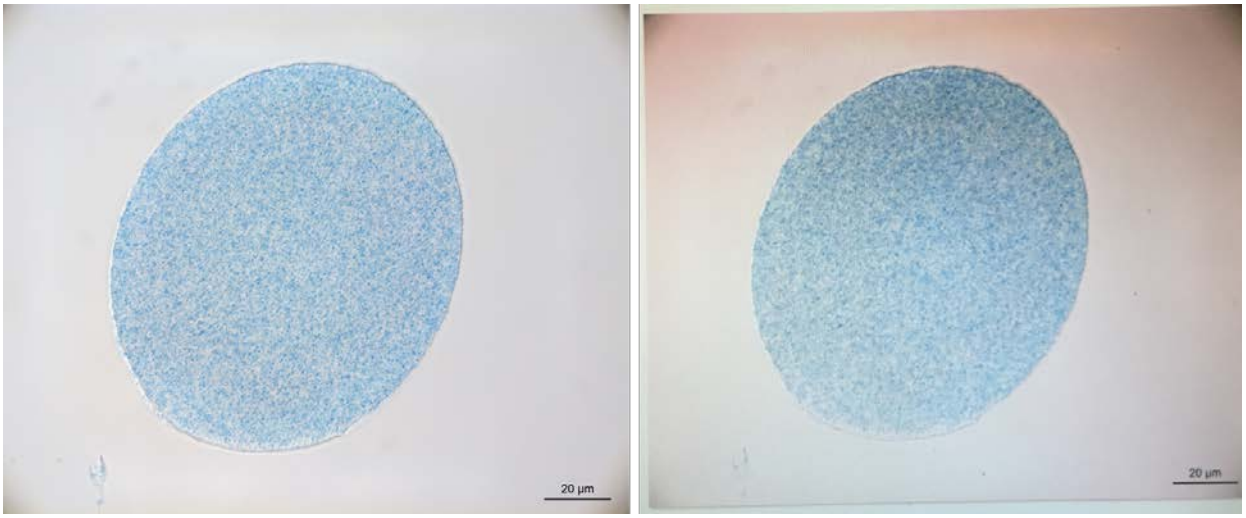

Figure 26. Same micrograph image of pristine PROLENE shown on two different computer monitors. A photograph of the image on the screen of monitor 2 was taken to preserve the observed pink coloring artifact. Sample was produced as part of the work described in Appendix H

Thickness Variation and Stain Pooling

When high aspect ratio samples (such as fibers) are sectioned with a microtome, simple geometry dictates that the thickness will vary if the microtome blade is not orthogonal to the sample's long axis. This geometric artifact is exhibited schematically in Figure 27A-D, which illustrates that the edges of the sliced specimen are thinner when viewed under the microscope.

This effect can result in stain pooling, which is also illustrated schematically in Figure 27E. The cylindrical fibers that compose the mesh (A) can be cut in an oval shape depending on the angle at which the blade encounters the fiber (B). When the resulting section (C) is placed on a glass slide and stained, the angle between the section and the glass forms a small pocket in which stain can accumulate (D), giving the appearance, including color, of "true" staining (E) – that is, of chemical interactions between dyes and their ligands. In reality, this is merely a mechanical entrapment of the stain.

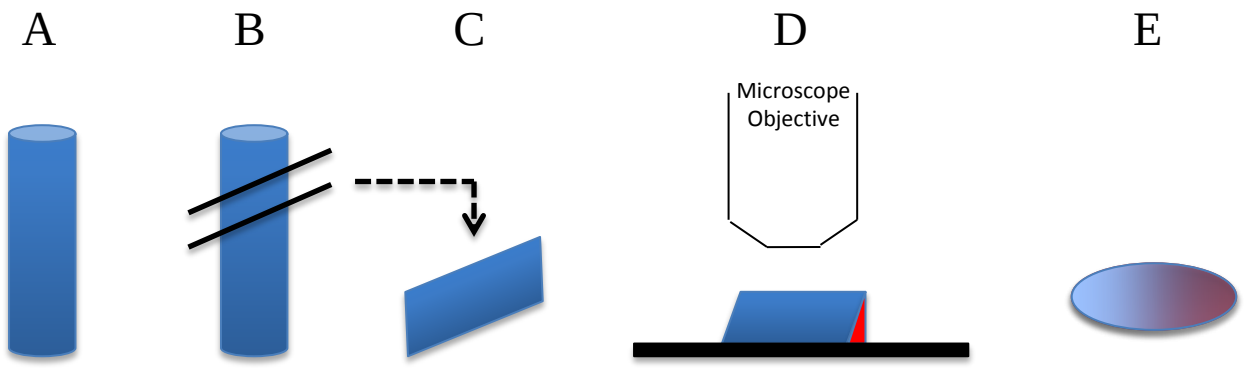

Figure 27. Potential formation mechanism of pooling artifact. A mesh fiber (A) can encounter the microtome blade at an angle (B), forming a section with an angled ledge (C), under which stain can pool (D) and give the appearance of true staining (E).

Stain pooling was observed in several fiber cross sections examined as part of this study. An example of stain pooling, as observed in a pristine TVT device not expected to stain, is given in Figure 28. Different planes of focus for the fiber cross section are given in Figure 28 that include an image of the plane of the fiber nearest the reader in focus (a) and the plane farther away from the reader, underneath the pristine fiber where the stain is pooled (b).

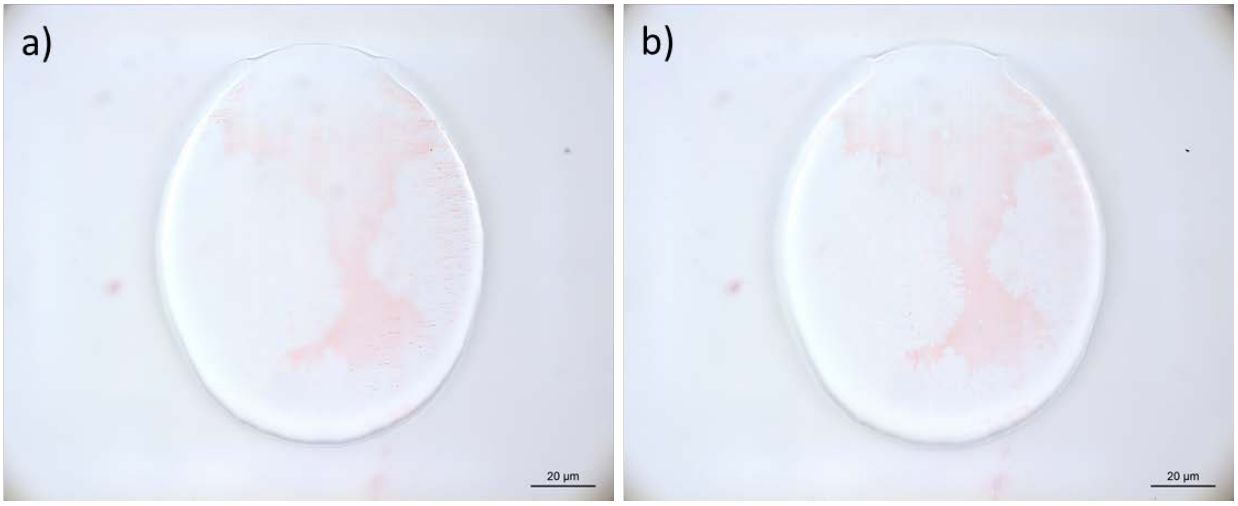

Figure 28. Example of stain pooling is shown from a sample prepared as part of the work described in Appendix H. A fiber cross section from a pristine TVT mesh, not expected to stain, is shown with different planes of focus. For image a), the plane nearest the reader is in focus. For image b), the stain pooled underneath the fiber is in focus.

Polarizing Artifact

Polarized microscopy is a powerful tool in polymer science.[140] With good optics and proper alignment, it allows for the visualization of anisotropic structures, making them appear under varying shades of brightness with a polarizing filter in the microscope's light path.[141] The brightness of the sample when imaged under polarization depends on factors including sample alignment. The brightness is highest when the object is aligned at a 45^{o} angle to the polarizers. On the other hand, the object can become difficult to see when aligned parallel to one of the two polarization planes.[141]

The thickness variation resultant from microtoming, as well as the tendency of an anisotropic fiber to tear away from a surrounding matrix, can create edge artifacts under polarized light. An

[140] Lenz, R. W. Experiments in Polymer Science, Edward A. Collins, Jan Bares, Fred W. Billmeyer, Jr., Wiley-Interscience, New York, 1973.

[141] Wolman, M. Polarized Light Microscopy as a Tool of Diagnostic Pathology. *J. Histochem. Cytochem.*, (1975) 23(1):21–50.

example of such an artifact is displayed in Figure 29, which is a micrograph of an *unoxidized* (no possible "bark") pristine PROLENE mesh fiber subjected to H&E staining. In Figure 29b and Figure 29c, the fiber is shown under polarized light, and a dark ring of false "bark" is visible on a portion of the fiber exterior. The images in Figure 29 show the same region with and without the polarizer.

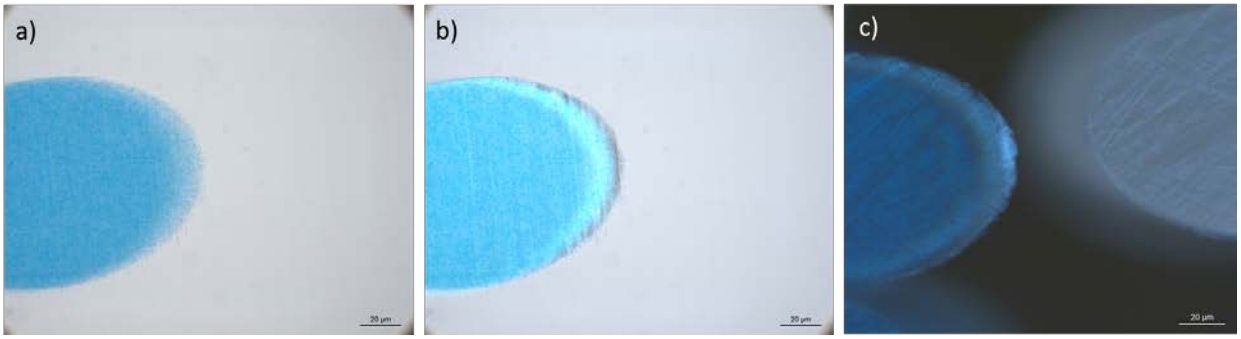

Figure 29. Pristine, unoxidized PROLENE mesh after staining with H&E produced as part of the work described in Appendix H. Image (a) was obtained without polarized light. Image (b) was acquired with plane-polarized light and (c) with cross-polarized light.

Becke Lines

Differences in refractive indices (material density) between a transparent specimen and its surroundings can cause the appearance of light and dark parallel lines at the interface between materials. These lines are known in microscopy as Becke lines.[142] Figure 30 illustrates this imaging artifact at the edge of a QUV oxidized PROLENE mesh cross section embedded in paraffin and subjected to H&E staining. The relative location and thickness of these lines change based on the position of the focal plane with respect to the surface of the microscopy slide, with the thinnest line corresponding to the microscope being focused at the surface. These lines can be altered by changing the focus in the microscope[142] as seen in the videos included in Appendix F.

[142] Zalevsky, Z., Sarafis, V., "Phase Imaging in Plant Cells and Tissues," *Biomedical Optical Phase Microscopy and Nanoscopy*, chapter 4. Oxford, UK: Elsevier, 2013.

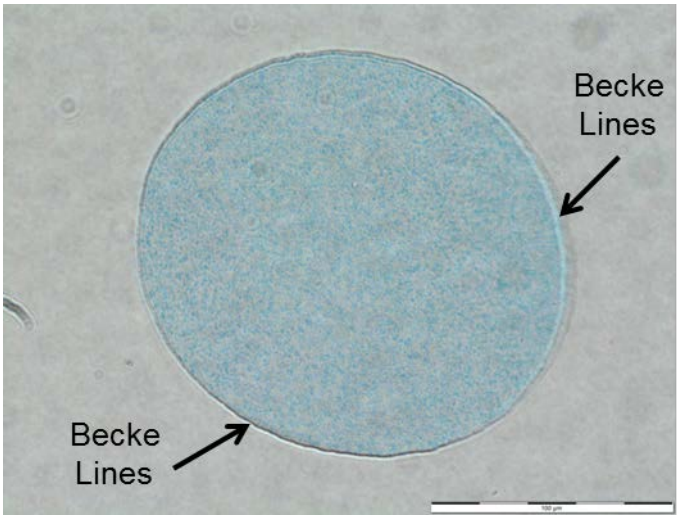

Figure 30. QUV oxidized PROLENE mesh embedded in paraffin, and subjected to the H&E staining protocol. Notice dark and light Becke lines around the fiber perimeter.

Purple Hue

Additional imaging artifacts can be created due to changes in incident light. For example, the artificial faint purple hue observed in discrete locations of the specimen shown in Figure 31 (right) is the consequence of exposing the specimen to plane-polarized light. It is evident that this hue is an artifact of the imaging technique due to its absence when the same specimen is examined with the same microscope at the same magnification under non-polarized light (left).

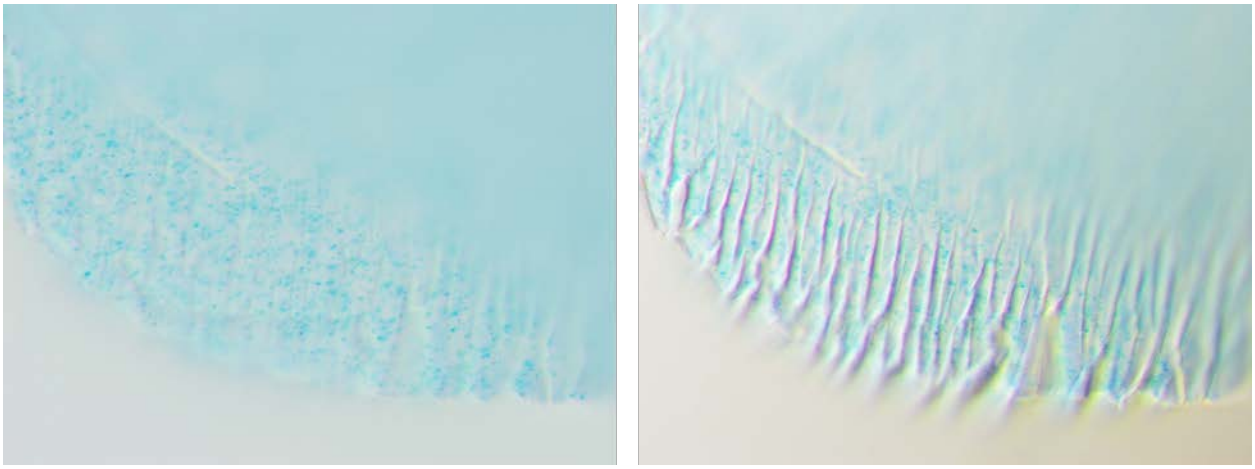

Figure 31. QUV oxidized PROLENE mesh embedded in paraffin, subjected to the H&E staining protocol, and imaged with non-polarized light (left) and plane-polarized light (right). No staining is evident. The purple hue (right) is an artifact of the imaging technique.

Blue Granules Outside Fiber Boundary

Due to the cylindrical nature of the fibers, if a cross section is not cut perfectly orthogonal to the fiber's long axis, the resulting slice will be slightly skewed as seen in Figure 32 (left). When this fiber is viewed from the top through the microscope, the blue granules beneath the top surface of the fiber cross section appear to extend beyond the fiber boundary, as shown schematically in Figure 32 (right). The Becke lines indicate the outline of the fiber at the surface of the microscope slide. An example of this artifact can be seen in Figure 33, where an unoxidized exemplar PROLENE mesh was mounted in paraffin, cross sectioned and subjected to the H&E staining protocol. When examined with the optical microscope, the fiber exhibits this artifact manifested by the appearance of blue granules extending beyond the fiber boundaries.

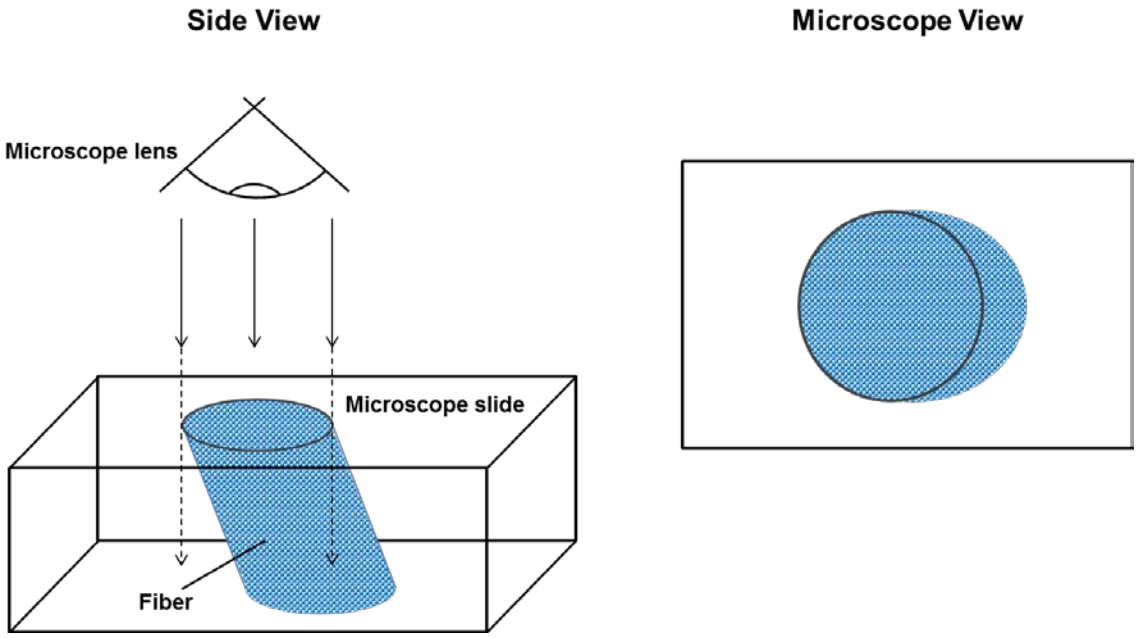

Figure 32. Schematic of proposed artifact mechanism where blue granules appear outside the fiber boundary. If a fiber is cut at an angle (left) and the cross section is viewed from the top through the microscope lens (right), it can appear that the blue granules extend beyond the fiber boundary.

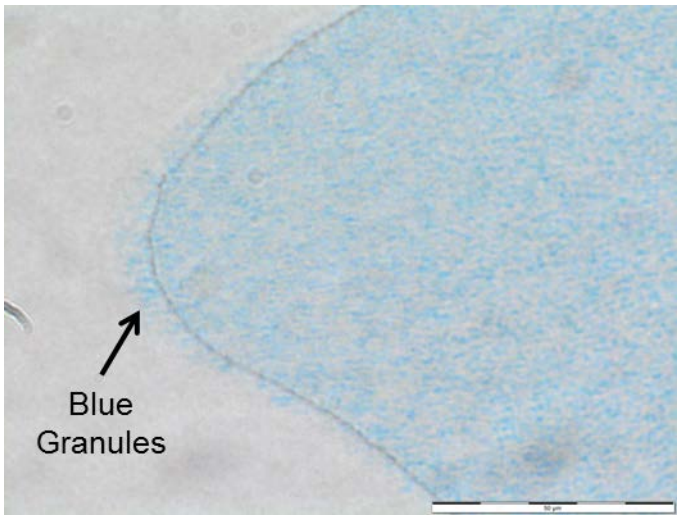

Figure 33. Unoxidized exemplar PROLENE mesh embedded in paraffin, and subjected to the H&E staining protocol. Note the appearance of blue granules beyond the perimeter of the fiber.

Rebuttal of Plaintiff Experts

Iakovlev

Exponent reviewed the reports authored by Dr. Vladimir Iakovlev[143,144] and disagrees with several of his findings, opinions and methodologies. The following section summarizes the issues encountered with Dr. Iakovlev's reports.

Dr. Iakovlev stated that, "Examination reveals a polypropylene degradation layer on the outermost layer of the mesh filaments."[145] Dr. Iakovlev performed absolutely no chemical characterization of the external surface to verify his assertion that the layer is polypropylene, much less degraded polypropylene.

Dr. Iakovlev's assertion that the bark layer is comprised of PROLENE is sheer speculation based on his qualitative observation that the bark illuminates when exposed to cross-polarized light. Any material possessing anisotropic domains has the potential to become visible when examined under cross-polarized light. In fact, Dr. Iakovlev has clearly demonstrated that stained biological material (collagen), with presumably a low degree of molecular order, has the ability to illuminate when microscopically imaged under cross-polarized light. The results from his polarized light experiment, at best and at most, suggest that the bark layer contains crystalline domains (local ordering of molecules) within its structure. In short, these results do not confirm the "bark" layer is synthetic, nor does it conclusively prove the layer is PROLENE.

According to the GPC data generated during the Seven Year Dog Study (Table 1), none of the explanted PROLENE sutures exhibited any signs of degradation after seven years *in vivo*. No discernible differences were observed in any of the molecular weight values between

[143] Iakovlev MDL Consolidated Case Report dated 8-24-15.

[144] Iakovlev Wave 1 General Report with attachments dated 1-29-16.

[145] Iakovlev MDL Consolidated Case Report dated 8-24-15, pg 17.

unimplanted control sample material and explanted sample material. Moreover, Dr. Iakovlev did not perform any testing that attempts to quantify losses in PROLENE molecular weight, which is the ultimate determination of polymer degradation. Without having generated this data on material from PROLENE control specimens and explanted specimens, any opinions rendered by Dr. Iakovlev that are related to PROLENE degradation are unreliable.

For long-chain, linear polymeric materials such as polypropylene (PROLENE based polymer) the term degradation is synonymous with a reduction in the polymer's molecular weight.[146] When polymers suffer losses in molecular weight, measurable changes in bulk physical properties such as elongation at break are realized. In light of these fundamental polymer science concepts, the data generated by Ethicon during its Seven Year Dog Study is clear. None of the tested PROLENE sutures explanted from the subject dogs showed any signs of molecular weight loss or tensile property loss when compared to control samples.[84,106] In fact, the *in vivo* environment had a positive effect on the PROLENE's tensile properties. In particular, the elongation (also referred to as ductility or toughness) increased over the seven year testing period and ultimately achieved strain-at-break values of approximately 80% (an increase of 111% over unimplanted controls).[106] To put this value in perspective, the PROLENE explanted specimens, on average, almost doubled (1.8x) in length prior to breaking during the tensile test. In contrast, polymeric materials that truly exhibit brittle behavior have strain-at-break values less than 2%, meaning they are capable of extending by a only 2% of their original length prior to breaking during a tensile test. When the data is viewed in totality, it is clear that the PROLENE did not suffer from material degradation and did not become embrittled.

Dr. Iakovlev also opined that PROLENE mesh becomes brittle and, as a consequence, also becomes stiffer with time spent *in vivo*. These opinions are subjective as they are based solely on Dr. Iakovlev's visual observations of the microcracking and the tactile feel of explanted, and perhaps formalin-fixed, bulk tissue and PROLENE mesh specimens. Estimating a material's

[146] Fried, J.R., Polymer Science and Technology 2nd edition. Prentice Hall Professional Technial Reference, Upper Saddle River, NJ, 2003.

"stiffness" or change in "stiffness" by manually manipulating a specimen is not an accepted scientific method within the material science community. Moreover, Dr. Iakovlev has not performed any testing to quantify any perceived increase in stiffness; therefore these assertions are both speculative and baseless. Scientifically reliable test methods exist that quantitatively assess a material's inherent stiffness, namely tensile testing, which determines the stiffness (modulus) of a material of known dimensions based on load-deflection or stress-strain data. In fact, tensile testing on explanted PROLENE sutures was performed by Ethicon at the one year, two year, and seven year time intervals during its Seven Year Dog Study.[106] The results of these tests were conclusive; the explanted PROLENE material not only became tougher and more ductile over time, but also became *less* stiff based on the reduction in modulus as a function of time *in vivo*. The results are also in complete contradiction to Dr. Iakovlev's assertion that the "degradation of polypropylene with resultant stiffening of the mesh is progressive over the years."[147]

Dr. Iakovlev opined in a recently published article that "[a]lthough the degraded layer is thin in relation to the fiber diameter, its circumferential distribution provides the highest mechanical effect on the mesh fibers. Degradation related stiffening of the mesh is expected to increase over time."[148] Dr. Iakovlev also noted that his alleged "bark" layer showed nanocavities (cracks) that indicate brittleness.

From a fundamental polymer science perspective, Dr. Iakovlev's above-stated opinions are flawed for a number of reasons. First, if we assume, that the "bark" layer is stiffer than the underlying material and that it is filled with cracks (or nanopores and nanocavities as Dr. Iakovlev calls them), it is by definition discontinuous and therefore mechanistically cannot contribute to an increase in stiffening.[149] Dr. Iakovlev cannot have it both ways, either the

[147] Iakovlev MDL Consolidated Case Report dated 8-24-15, pg 13.

[148] Iakovlev, V. V., Guelcher, S. A., Bendavid, R. Degradation of Polypropylene *in Vivo*: A Microscopic Analysis of Meshes Explanted from Patients. *J. Biomed. Mater. Res. B Appl. Biomater.*, (2017) 105(2):237–248.

[149] Had he chosen to do so, with even a fundamental knowledge of mechanics, Dr. Iakovlev could have easily calculated that a continuous (without his observed pores and cracks) bark of the thickness he has measured could not meaningfully contribute to an increase in mesh stiffness.

material is stiff and uniform and leads to mesh stiffening, or it cracks and forms pores and traps dyes; the two are mutually exclusive. Second, if the polypropylene is actually being broken down into smaller molecules, it will tend to become less stiff, not more. Again, Dr. Iakovlev cannot have it both ways (indeed, by stating degradation into smaller molecules leads to stiffening, Dr. Iakovlev underscores the flawed nature of his reasoning).

Dr. Iakovlev presented a short-term control study to show that formalin will not cause a degraded layer to form on PROLENE mesh. His study consisted of immersing pristine PROLENE samples in formalin for four months followed by embedding in paraffin and staining. Dr. Iakovlev stated that this control showed an "absence of degradation after exposure to formalin and chemicals of tissue processing,"[150] due to the lack of a "bark" layer formation. This control experiment is scientifically unjustified as he neglected the potential contribution of biological materials on the formation of the "bark" layer. If the "bark" were biologic in nature, it would be necessary to not only expose the fibers to formalin but also biological material to evaluate the experimental design space. Excluding one of the potential experimental factors that may contribute to "bark" formation invalidates the findings from his *in vitro* control experiment. In addition, even if he had included all the necessary components for this control experiment, the time period of this study was approximately an order of magnitude (10x) shorter than the length of time explanted samples are stored in formalin and therefore is inadequate.

Dr. Iakovlev used the "bark" thickness increase with time *in vivo* as further evidence that the "bark" is degraded PROLENE.[151] In his analysis, he completely ignored the possibility that a biological material covering the PROLENE mesh could also increase in thickness with time; creating a crust that will correspond in thickness to the biological material deposited *in vivo*. Furthermore, Dr. Iakovlev did not specify his process for measuring the crust layer on his explants. Histological slides have very few, if any, completely circular fiber cross sections. Unless each measurement was taken at the exact minimum diameter location on each sample

[150] Iakovlev MDL Consolidated Case Report dated 8-24-15, pg 17.

[151] Iakovlev MDL Consollidated Case Report dated 8-24-15, pg 82.

(i.e. the long axis of fiber is perpendicular to the direction of the microtome blade), his results may not be reliable. The presence of a time-dependent bark thickness is not indicative of the composition of the bark.

No basis has been provided for Dr. Iakovlev's suggestion that oxidized PROLENE will stain with Hematoxylin and Eosin (H&E). He neglected to perform an appropriate control experiment or provide scientific rationale to support his implication that his staining technique is appropriate to differentiate between the purported oxidized PROLENE bark layer and the inner core of the same fiber, as demonstrated in the experiments described previously. Without a proper control, Dr. Iakovlev's claims are based on flawed and untested hypotheses. Furthermore, H&E stain will adhere to any material with acidic or basic functional groups, which are commonly found in biologic materials. If anything, the staining shows that the crust layer is more likely biologic in nature than oxidized PROLENE.

Dr. Iakovlev further opined that the trapping of histological dyes in 'nanocavities' somehow indicates degradation due to a decrease in pore size farther from the outer surface of the crust layer. This experiment is wrought with faults that are contradicted by Dr. Iakovlev's own report and also suffer from a lack of controls. The basis for this experiment is that a dye of smaller size will be able to penetrate further into the bark layer due to the presence of supposed nanocavities that purportedly decrease in size as they approach the PROLENE core. Dr. Iakovlev provided no justification or reasoning that nanocavities would exist on the size scale that would be selective to the size difference of the molecules, nor does he provide the size difference between the staining molecules. In his limited description of the experiment, which is not fully documented within the report, Dr. Iakovlev again failed to provide any control materials with known pore sizes or with varying conditions to demonstrate the possibility of this size selectivity. Additionally, Dr. Iakovlev used multiple stains throughout the course of his investigations, including H&E. Assuming Dr. Iakovlev's hypothesis was correct and there were pores capable of size selecting for these stains and assuming chemical adsorption did not occur,

H&E stain would show the same size exclusion as the trichrome stain. This does not happen, indicating that the idea of pore size selection based on molecular size is not occurring.

Dr. Iakovlev opined that microcracking of the PROLENE mesh fibers occurs *in vivo*, but failed to consider the possibility that the microcracking could occur during the explantation process. To the best of Exponent's knowledge, all observations of surface microcracking by numerous researchers have been made on explanted meshes.[45,49,50,58,59] In addition, an Ethicon study determined that explanted mesh material, maintained and examined under wet conditions showed little, if any, signs of cracking while wet samples that were allowed to dry under ambient conditions developed cracks. In fact, the report states that the "[s]utures kept in the wet state do not exhibit cracks. Upon drying, cracks appear – this was actually observed happening by drying '83–165 6 yr. wet' on the microscope stage."[87] It is possible that the microcracking observed by Dr. Iakovlev in PROLENE mesh "immediately after explantation from the body"[152] resulted from exposure to ambient conditions, mechanical stress imposed on the mesh during explantation, or a combination of both.

Dr. Iakovlev further opined that the retention of blue particles within the "bark" material covering the blue fibers proves that the bark is degraded PROLENE. Unfortunately, he failed to consider an important aspect of the sample preparation procedure which may account for this result. These samples were microtomed, or sliced very thinly with a knife. Although microtoming is a well-utilized specimen preparation technique within the scientific community, it is essential to be aware of the well-documented artifacts associated with the procedure. It is well-known in the scientific community that microtoming can cause tearing or smearing artifacts,[123] cutting defects,[125] structure deformations[153] and other sometimes difficult to identify artifacts.[124] In addition, blue granules in the "bark" can also be an artifact of a non-orthogonal cross section as demonstrated earlier in this report. The fact that the majority of the blue particles appear close to the polymer core of each image strongly suggests sample preparation

[152] Iakovlev MDL Consolidated Case Report dated 8-24-15, pg 17.

[153] Morgan, C. "Some Effects of the Microtome Knife and the Electron Beam on Methacrylate-Embedded Thin Sections." *J Biophysi Biochem Cyto*, (1956) 2(4 Suppl):21–28.

artifacts as opposed to a degraded "bark," as proposed by Dr. Iakovlev. If the "bark" was degraded PROLENE, the entrapped blue particles would be more uniformly present throughout the bark layer and not biased towards the inner surface.

Dr. Iakovlev stated, "[f]or nearly a half century, scientists around the world have studied polypropylene, including Ethicon's Prolene used in TVT product [sic] and have consistently found that polypropylene degrades over time after being implanted in the body."[154] Dr. Iakovlev used fifteen journal articles as references for this statement, but many of them have absolutely no relevance to *in vivo* oxidation of polypropylene. For example, the articles written by Schmidt,[155] Rosa,[156] and Blais[157] report on the *photo* oxidation of polypropylene, these articles in no way support Dr. Iakovlev's statement that polypropylene degrades *in vivo*. The use of irrelevant references at best shows Dr. Iakovlev's lack of polymer science education, training, and experience, and at worst, displays an attempt to artificially bolster his opinion with misleading references.

In his final opinions, Dr. Iakovlev claimed that the absence of a stainable outer layer encompassing the explanted nonpolypropylene materials he examined is further proof that the outer layer is degraded polypropylene. His rationale for this statement is that biologic material supposedly does not have varying degrees of affinity for diverse polymers. There are two reasons why this hypothesis is incorrect. First, the exact makeup of the biological material comprising the outer layer is unknown. Second, numerous studies have been published showing visual differences in the surface features between different explanted mesh materials (e.g. PDVF, PET, PTFE, etc.), including many cited in Dr. Iakovlev's own report.[45,58,59,75,110]

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[154] Iakovlev MDL Consolidated Case Report dated 8-24-15, pg 8.

[155] Schmidt, H., Witkowska, B., Kaminska, I., Twarowska-Schmidt, K., et al. "Comparison of the Rates of Polypropylene Fibre Degradation Caused by Artificial Light and Sunlight." *Fibres Text. East. Eur.*, (2011) 19(4):53–58.

[156] Rosa, D. S., Angelini, J. M. G., Agnelli, J. A. M., Mei, L. H. I. "The Use of Optical Microscopy to Follow the Degradation of Isotactic Polypropylene (iPP) Subjected to Natural and Accelerated Ageing." *Polym. Test.*, (2005) 24(8):1022–1026.

[157] Blais, P., Carlsson, D. J., Clark, F. R. S., Sturgeon, P. Z., et al. "The Photo-Oxidation of Polypropylene Monofilaments: Part II: Physical Changes and Microstructure." *Text. Res. J.*, (1976) 46641–648.

Moreover, it is well understood in the polymer science community that different polymers with different molecular structures will have different physical and chemical attributes. Two such relevant attributes are the polymer's ability to permit foreign material (e.g. body proteins) to diffuse through or adsorb to its outer surface.

Jordi

Exponent reviewed the report authored by Dr. Howard Jordi[158,159] and disagrees with several of his methodologies, findings, and opinions. In particular, issues were found in both Jordi's interpretation of literature as well as his own research. The following section summarizes these issues.

Dr. Jordi carried out FTIR measurements on three samples (a PROLENE mesh explant, a pristine PROLENE fiber, and human albumin) to identify the presence of specific chemical functional groups which are indicative of oxidation in the explanted sample. He claimed the explanted sample contains oxidized regions of PROLENE based on the presence of an absorbance peak at 1761 cm^{-1}, which he attributed to carbonyl functionality. However, he did not discuss the amide I and amide II peaks that are clearly present at 1650 and 1550 cm^{-1} respectively, which also appear for the human albumin sample, and are indicative of a biological material. Amide bonds are inherent to proteins and are the units that link amino acids together; many biological materials would be expected to exhibit both of these amide peaks as well as a carbonyl peak. In addition, Dr. Jordi attributed a peak at 1761 cm^{-1} as evidence of oxidation; however, he did not discuss how he differentiates this peak from the peak associated with the carbonyl containing groups in fatty acid esters which Dr. Jordi claimed have "absorbed into the TVT devices."[160]

[158] Jordi MDL Consolidated Case Report dated 8-24-15.

[159] Jordi Wave 1 Expert Report dated 2-1-16.

[160] Jordi MDL Consolidated Case Report dated 8-24-15, pg 23.

There are several instances in which Dr. Jordi failed to mention, reference, or explain figures that are in his report. One such example can be seen in Figure 8, it is unknown what, if any, conclusions are intended to be drawn since the sample description, procedure used, and observations are absent. If Dr. Jordi's intention was to demonstrate the presence of oxidation in this sample from the FTIR absorbance peak observed at 1740 cm^{-1}, then this conclusion is unsupported since, as discussed previously, he did not provided a method to differentiate between other sources of carbonyl-containing compounds which may be present on or in the explanted PROLENE fibers.[8]

Dr. Jordi used nanothermal analysis to attempt to determine the surface melting point of pristine and explanted PROLENE mesh fibers. Part of the commonly accepted procedure when using this technique, is to calibrate the temperature of the cantilever as a function of resistance. Dr. Jordi calibrated the cantilevers utilized in this experiment using the melting points of polyethylene terephthalate, polyethylene, and polycaprolactone.[161] His justification for using these samples as calibration standards was his reference to Nelson, *et al.*[162] However, based on their work in determining a proper calibration procedure, Nelson *et al.* state that "the use of organic melting standards is thus ineffective for temperature calibration of silicon-heated cantilevers having extremely sharp tips." Since Dr. Jordi's referenced calibration procedure directly states not to use the sample type Dr. Jordi used for his calibration, the calculated melting point values cannot be relied upon as accurate. It is unclear what the offset from the reported values should be since the relationship between bulk and surface melting temperatures is nonlinear.[162]

Even if the values reported by Dr. Jordi were accurate, the conclusion drawn from them would be incorrect. Dr. Jordi reported an average melting temperature of the Bellew explanted samples of 124 °C, compared to 176 °C for the pristine non-explanted control samples. According to Dr. Jordi, the over 50 °C decrease in observed melting temperature can be considered proof of

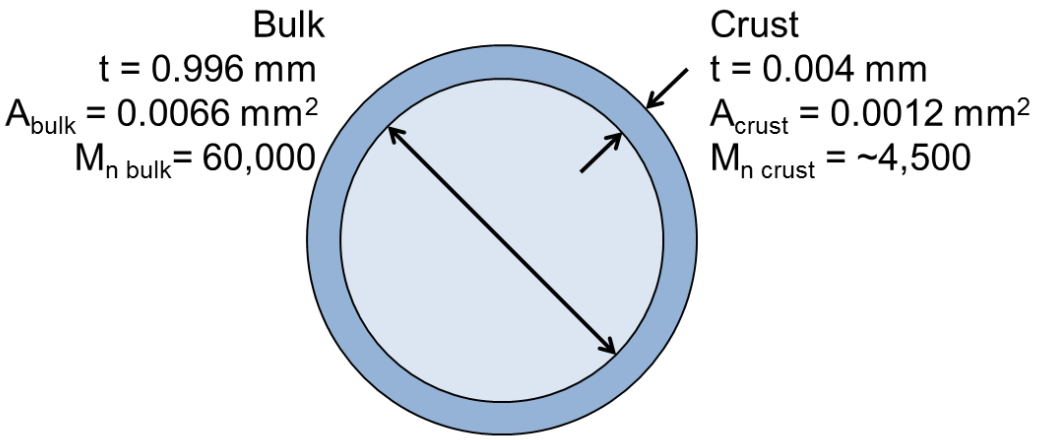
[161] Jordi Bellew Report dated 7-7-14.

[162] Nelson, B. A., King, W. P. "Temperature Calibration of Heated Silicon Atomic Force Microscope Cantilevers." *Sens. Actuators Phys.*, (2007) 140(1):51–59.

sample oxidation. This is incorrect for two reasons. First, surface oxidation of a fiber would result in a decrease in molecular weight. An isotactic polypropylene sample with a melting temperature of 124 °C would correspond with a M_n of roughly 4,500.[163] A decrease in molecular weight of this magnitude of the surface material would be apparent in bulk molecular weight measurements of the explanted samples. If one assumes that the cracked region has a depth of 4 μm[143,164] and is uniformly distributed over the surface of 5-0 sutures as seen in the Seven Year Dog Study (suture diameter of 0.1 mm), then the bulk PROLENE M_n should drop from 60,000 in the pristine sample[84] to approximately 51,000 (see Figure 34). However, from the bulk molecular measurements made in the Seven Year Dog Study, it is known that the molecular weight of explanted sutures is 61,000 ± 6,000.[84] Since the molecular weight according to Dr. Jordi is below the statistically predicted range of values, it is unlikely that oxidation is the cause of the melting temperature drop. The second issue with his conclusion is that Dr. Jordi did not consider alternative explanations for this decrease. The decrease in melting temperature could also be caused by tissue or small molecule plasticizers[105] that are preferentially on or adhered to the outside diameter surface of the fiber, but these factors were not explored by Dr. Jordi.

[163] Natta, G., Pasquon, I., Zambelli, A., Gatti, G. "Dependence of the Melting Point of Isotactic Polypropylenes on Their Molecular Weight and Degree of Stereospecificity of Different Catalytic Systems." *Makromol. Chem.*, (1964) 70(1):191–205.

[164] 11 – "Crack Depth in Explanted PROLENE Polypropylene Sutures" memo 1982.06.15 (ETH.MESH.12831405-12831406).



$$M_{n\ total} = \frac{(A_{crust} \times M_{n\ crust}) + (A_{bulk} \times M_{n\ bulk})}{A_{total}}$$

$$M_{n\ total} = \sim 51{,}000$$

Figure 34. Cross sectional schematic and calculated theoretical total molecular weight (M_n) of excised 5-0 PROLENE sutures from Ethicon's seven year dog study using Dr. Jordi's surface melting temperature to calculate M_n of the crust layer (note: dimensions are not to drawn to scale).

Dr. Jordi reviewed Ethicon's internal documents, including the Seven Year Dog Study, and concluded that PROLENE degrades *in vivo*. While these documents have already been discussed in the body of this report, several statements from Dr. Jordi were found to be in error and will be discussed herein.

In the process of summarizing Ethicon's documents, Dr. Jordi highlighted FTIR data taken by Ethicon, in which Ethicon mentioned the possibility that a weak peak at 1650 cm^{-1} could be attributed to slight oxidation. However, in the very next paragraph of Dr. Jordi's report, he contradicted his observation, stating "[t]he 1650 cm^{-1} and 1540^{-1} cm bands are typically indicative of what are known as the amide-I and amide-II bands respectively of the polyamides."[165] These bands, as discussed above, in this context, are suggestive of proteins or other biological materials.

[165] Jordi MDL Consolidated Case Report dated 8-24-15, pg 14.

Dr. Jordi believed that a "polypropylene mesh placed in the pelvic region of a woman's body will undergo greater degradation than polypropylene placed in the heart of a dog."[165] His basis for this opinion is several articles discussing the bacterial concentrations typically found in this part of the body. In order to make such a statement, Dr. Jordi would need to compare this environment with that of the heart of a dog. He makes no such comparison and his opinion is not based on scientific facts.

Dr. Jordi analyzed the cracked regions of explanted PROLENE mesh devices through SEM imaging to demonstrate that fibers had undergone oxidative degradation. However, Dr. Jordi did not remove the biological material from his samples, which can clearly be seen in Figures 11, 12, and 14 of his report. As such, he did not account for the fact that the cracked surface may in fact be biological in nature. Furthermore, Dr. Jordi did not present data that identifies the composition of the cracked regions (EDS, FTIR, GPC, or nanothermal analysis). Therefore, while visual observations can be made from these images, no definitive conclusions regarding the composition of the cracked material can be drawn.

Dr. Jordi further opined that the antioxidant DLTDP leaches with time, his sole evidence for this presented in his report dated August 17, 2015, is from intensity differences in FTIR measurements conducted by Ethicon. As discussed in detail in the Microcrack Committee Investigation section, an independent analysis of the FTIR spectra would lead to the conclusion that it is impossible to isolate spectral contributions from DLTDP since the carbonyl peak could also be due to proteins and other biological compounds. In addition, the FTIR data generated by Ethicon cannot be used to reliably quantify functional group concentrations in a sample material in the absence of a calibration study with corresponding calibration curves. No such calibration study was noted in the reviewed Ethicon documents and no such study was independently performed by Dr. Jordi. Therefore, Dr. Jordi's opinion regarding the in vivo leaching of DLTDP is scientifically baseless and, in turn, unreliable.

Dr. Jordi made the unsubstantiated claim that "a vast majority of scientists who have studied polypropylene for degradation have consistently concluded that polypropylene (including PROLENE) undergoes *in vivo* degradation"[166] without citing the documents with which he drew this conclusion.

Dr. Jordi stated in his opinions that *in vivo* degradation causes PROLENE to become brittle. However, he never once discussed the topic of embrittlement in the main text of his report, nor did he perform or cite any mechanical testing to support his opinion, which left it unclear as to how this conclusion is reached. Furthermore, this opinion is completely contradictory to the results of the tensile testing experiments presented in Ethicon's Seven Year Dog Study.[106]

Another of Dr. Jordi's opinions is that the manufacturing process leaves PROLENE susceptible to environmental stress cracking (ESC). It is unknown on what Dr. Jordi based this statement, since there is no mention of the manufacturing process in the text of his report, and thus this opinion is completely unsupported.

In Dr. Jordi's final opinion, he stated that cholesterols and fatty acids absorbed by the PROLENE mesh leave it susceptible to ESC. His entire basis for this claim is his reference to Clavé's conclusion that "the diffusion of organic molecules into the polymer (especially esterified fatty acids or cholesterol) *may* (emphasis added) be a cause of the polymer structure degradation."[45] Dr. Jordi failed to realize that a polymer suffering from ESC will be embrittled,[167] resulting in a decrease in elongation at break, which directly contradicts the results of Ethicon's Seven Year Dog Study.[107] Additionally Dr. Jordi neglected to perform any original research or literature review on this topic and relies solely on conjecture and hypothesizing to form his opinions and therefore his opinion should not be considered scientifically valid.

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[166] Jordi MDL Consolidated Case Report dated 8-24-15, pg 23.

[167] Wright, D. C., Rapra Technology Limited. *Environmental Stress Cracking of Plastics*. Shrewsbury: Rapra Technology, 1996. 3.

Mays

Exponent reviewed the report authored by Dr. Jimmy Mays[168] and disagrees with several of his findings, and opinions. Dr. Mays did not perform any experiments, but relied on the previously discussed works of Liebert,[57] Mary,[58] Costello,[50] Bracco,[75] Clavé,[45] Imel,[83] Iakovlev,[148] Wood,[59] and various Ethicon documents.[169]

Dr. Mays discussed the "cracked" layer observed on the exterior of explanted PROLENE fibers in both reference literature and Ethicon-produced documents, and inferred degradation, failing to recognize that cracking and degradation should not be treated as synonymous. In doing so, he fails to recognize the possibility that the cracked layer is composed of a different material than oxidized PROLENE.

Dr. Mays agreed that it is well-established in the polymer science community that esterified fatty acids are capable of plasticizing polymers. However, he takes the mechanism one step further by stating that the plasticization would likely facilitate "increased penetration into the PP fibers by oxygen and other oxidizing chemical species, thus accelerating PP fiber degradation due to oxidation."[170] However, Dr. Mays did not cite any scientific treatise that describes or affirms a subsequent oxidative degradation mechanism associated with fatty acid ester uptake. In short, his stated "accelerated oxidation mechanism" is purely speculative and unsupported by the literature.

In agreement with Thompson *et al.*,[171] Dr. Mays offered strong criticisms of Thames' 23-step cleaning technique stating that the cleaning protocol was "designed specifically to remove all

[168] Mays Wave 1 Report dated 1-12-16.

[169] EthMesh12831405, EthMesh 15955438-15955473, EthMesh 15958452, EthMesh 15406978, EthMesh 15958470, EthMesh 1595843, EthMesh 15958336, EthMesh 15958445, EthMesh 00000367, EthMesh 12831391-1404, EthMesh 12831407, EthMesh 09888220, EthMesh 05439518, EthMesh 12006257, EthMesh 12009027, EthMesh 00865322.

[170] Mays Wave 5 Report dated 5-22-17, pg 21.

[171] Thompson, M., Guelcher, S., Bendavid, R., Iakovlev, V., Ostergard, D. R. In Vivo Polypropylene Mesh Degradation is Hardly a Myth. Int. Urogynecol. J., (2017) 28:333–335.

detachable material nonselectively (including protein and degraded PP) from the surface of the mesh fibers."[171,172] However, Dr. Mays neglected two pieces of unequivocal evidence provided by the Thames study[86] which demonstrated that the removable layer was indeed biological. First, the cleaned explant PROLENE fibers after the extensive cleaning protocol revealed extrusion lines that are formed during the fiber manufacturing process. The extrusion lines on the cleaned PROLENE fibers were essentially identical to exemplar fibers. If the surface of the fibers had been oxidized and non-selectively removed by sonication, as suggested by Dr. Mays, these fibers would not have exhibited extrusion lines that are native to freshly manufactured fibers. Second, Thames *et al.* pointed out that the cracked/flaking material was clear or translucent regardless of whether it was on clear (colorless) or blue-colored fibers. This observation is critical because if the cracked material was indeed oxidized PROLENE, flakes from blue-colored fibers would be blue instead of clear/translucent. It is notable that Thompson *et al.* and Dr. Mays are silent on these two meaningful and relevant observations.

Dr. Mays continued his criticism regarding the cleaning protocol indicating that Dr. Thames omitted ultrasonic steps on intentionally oxidized fibers.[173] As mentioned in the previous section on "Exponent's Analysis of Cleaned Explanted Mesh," Exponent performed the same cleaning procedure, including all the sonication steps, on an explant and on an intentionally QUV-oxidized mesh sample. As demonstrated in the SEM images in Figure 13, after the complete 23-step cleaning protocol, the surface of the intentionally QUV-oxidized PROLENE mesh fibers appeared intact, similar to the explant mesh fibers after cleaning. Furthermore, the surfaces of all of the 75 cleaned explant mesh fibers of various PROLENE devices from different patients in the Thames study[86] were intact post cleaning. Therefore, Dr. Mays' criticism of the cleaning protocol is unfounded.

Dr. Mays also asserted that the FTIR spectrum in Dr. Thames' report of the exemplar before Xenon exposure exhibited a sharp peak at 1742 cm^{-1}. Although Dr. Mays correctly identified

[172] Mays Wave 5 Report dated 5-22-17, pg 22.

[173] Mays Wave 5 Report dated 5-22-17, pg 24.

this peak as being in the region of carbonyl peaks, he erroneously associated this peak as "indicative of oxidation."[174] As mentioned previously, the presence of antioxidant DLTDP would result in the detection of carbonyl functionality by FTIR. Therefore, it is simply impossible to suggest oxidation based on an FTIR peak alone.

Dr. Mays repeatedly emphasized the decrease in mechanical properties expected to accompany PROLENE degradation, including stiffening and embrittlement. However, he did not perform any mechanical testing or rely on any published testing of any explanted PROLENE material to support his claim. While Dr. Mays acknowledged that plasticization can be caused by "esterified fatty acids," and that Bracco *et al* [75]confirmed the presence of such molecules on explants, he failed to link *in vivo* plasticization of the mesh with the mechanical properties associated with this well-documented and understood polymer phenomenon.[175] In fact, the changes in mechanical properties observed during Ethicon's Seven Year Dog Study (decrease in stiffness, increase in elongation at break, decrease in breaking strength)[176] are consistent with plasticization of the PROLENE suture, and completely contradict Dr. Mays' theory of degradation.

Dr. Mays' claim that PROLENE mesh undergoes a reduction in molecular weight while *in vivo* is not supported by literature or PROLENE testing results. Dr. Mays ignored the two molecular weight studies performed on explanted PROLENE by the Plaintiffs' expert, Dr. Jordi,[85] and by Ethicon in the Seven Year Dog Study (Table 1), both of which directly contradict his claim of *in vivo* molecular weight reduction. Instead, Dr. Mays relied on the previously discussed work by Imel *et al.*[83] on explanted Boston Scientific mesh (not PROLENE). This study is not applicable to the current matter due to likely formulation differences in mesh materials between the two manufacturers.

[174] Mays Wave 5 Report dated 5-22-17, pg 24.

[175] Wypych, G. *Handbook of Plasticizers*. Burlington: Elsevier Science, 2013.

[176] Ethicon's Seven Year Dog Study (ETH.MESH.11336183) pg.155.

Priddy

Exponent reviewed the report authored by Dr. Duane Priddy[177] and disagrees with several of his methodologies, findings and opinions. In particular, issues were found in both Dr. Priddy's interpretation of established testing standards, as well as his own research.

Dr. Priddy performed DSC experiments on ten PROLENE exemplar meshes in an attempt to illustrate variability in oxidation resistance among mesh lots. In doing so, he claimed that oxidation induction time (OIT) varied by 150% among the samples, which he attributed to variability in antioxidant concentration. Dr. Priddy claimed that his DSC testing followed the procedure detailed in ASTM D3895,[178] and specifically stated that the testing did "not deviate from the protocol listed in this testing procedure."[179] However, Dr. Priddy's report indicates that there were deviations from the protocol, and it is possible that these deviations, as described below, contributed to the variability in Dr. Priddy's test results, and not necessarily the samples themselves.

The standard recommends preparing samples by melting the material into a solid disk of consistent size and weight prior to testing. Presumably, this is to facilitate uniform thermal and atmospheric conditions to the sample, as well as to provide consistency among samples. Instead, Dr. Priddy stated that he placed "a small (~10 milligrams) fiber of the mesh inside a very sensitive instrument called a differential scanning calorimeter (DSC)." This implies that the sample geometry did not meet the ASTM standard recommendation. A deviation from the standard of this nature could lead to variability in OIT. Dr. Priddy's DSC data analysis method also differed from the ASTM standard in ways that may statistically alter the OIT values obtained. The exothermic peaks in his data likely come from two types of thermal events. The large exotherm at the end of each scan can likely be attributed to degradation of polypropylene.

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[177] Priddy Wave 1 Report.

[178] ASTM D3895-14, Standard Test Method for Oxidative-Induction Time of Polyolefins by Differential Scanning Calorimetry, ASTM International, West Conshohocken, PA, 2014, www.astm.org.

[179] Priddy Wave 1 Report, pg 3.

The smaller, intermittent peaks are likely the result of antioxidants and other additives present in the PROLENE sample being consumed, as stated in Note 12 of ASTM D3895.[178] Dr. Priddy does not consider this possibility during his analysis, as evidenced by the statement, "[a]s long as the antioxidants are present in the sample protecting the PP against oxidation, no exotherm is detected."[177]

In accordance with ASTM D3895, Dr. Priddy correctly defined OIT as the intersection of the baseline and a line drawn from the steepest linear slope of the exotherm.[178] However, as described in Note 12 of the ASTM standard, when additives are used, the slope of the polypropylene exotherm may not be smooth. This is the case for the majority of Dr. Priddy's reported data (samples 3, 5, 6, 7, 8, 9 and 10). To that end, Note 12 of the ASTM standard recommends resampling and retesting to "ensure that the testing is representative of the oxidation process."[178] Note 13 of the ASTM standard also states that "[i]f multiple slopes result from the oxidation process, OIT needs to be defined to accurately reflect the oxidation of the polymer." None of these recommendations were correctly applied by Dr. Priddy. An illustration of these shortcomings in Dr. Priddy's work can be seen in his analysis of samples 9 and 10. These samples were taken from the same model and lot number, and can be reasonably expected to have a similar additive content. However, the tangent lines used to determine OIT correspond to different features of the curves, meaning that comparison of Dr. Priddy's obtained OIT values will likely lead to false conclusions.

Dr. Priddy also used the value of "Incipient Oxidation Time" or "Incipient Surface Oxidation Temperature" (ISOT) to compare his DSC data. There are several issues with both his determination and use of these values. First, it is unknown what this value physically represents since it was (1) not referenced, (2) absent in any literature that I have encountered on this topic, (3) not included in the ASTM standard,[178] and (4) similarly defined to OIT according to the ASTM standard. Regarding the last point, the ASTM standard defines OIT as the "onset of the exothermic oxidation of a material." This is remarkably similar to Dr. Priddy's definition of ISOT, "the point at which the surface of the mesh shows evidence of incipient oxidation."

Secondly, even if this value had some meaningful significance, his determination of the value is incorrect. Assuming the material being oxidized at the smaller initial peaks was polypropylene, his determination of that time point is incorrect. As previously discussed, additives included in the sample can result in multiple peaks and slopes in the DSC curve. Dr. Priddy mistakenly assigns these features to the oxidation of polypropylene.

Lastly, even with the assumption that the initial exothermic peaks correspond to the oxidation of polypropylene, Dr. Priddy does not employ a consistent analysis method in his determination of ISOT values. For example, there are exothermic peaks in his curves for samples 4, 5, 6, and 9 at time points earlier than his determined ISOT, while ISOT values obtained for samples 2, 3, 7 and 8 are taken from the first observed peak. The inconsistency of this analytical procedure will likely lead to variable values and unreliable conclusions.

In addition to the issues with Dr. Priddy's DSC data analysis, he made several unfounded conclusions based on that data. These conclusions stem from his misapplication of the purpose and scope of any results obtained following ASTM D3895. The standard explicitly states in multiple instances that "OIT is a qualitative assessment of the level (or degree) of stabilization of the material tested."[178] Additionally, the standard states that no "definitive relationships [have] been established for comparing OIT values on field samples to those on unused products, hence the use of such values for determining life expectancy is uncertain and subjective." A possible reason for this limitation may be because the testing environment (i.e. pure oxygen) is expected to be different from the end-use environmental. Furthermore, accelerated aging tests of polypropylene do not follow a linear trend[180,181] and cannot be applied in the manner implemented by Dr. Priddy.

[180] Woo, L., Khare, A.R., Sanford, C.L., Ling, M.T.K., and Ding, S.Y., 2001, Relevance of High Temperature Oxidative Stability Testing to Long Term Polymer Durability: *Journal of Thermal Analysis and Calorimetry*, v. 64, no. 2, p. 539–548.

[181] Woo, L., Ling, M., Khare, A.R., and Ding, Y.S., 2001, Polypropylene Degradation and Durability Estimates Based on the Master Curve Concept, *in* Ageing Studies and Lifetime Extension of Materials, Springer US, p. 499–506.

In particular, Dr. Priddy attempted to use OIT values obtained using the ASTM standard to predict approximate times to oxidative degradation. In doing so, he made several scientifically unsubstantiated statements about the validity of PROLENE as a permanently implantable medical material.

Dr. Priddy attempted to correlate the levels of antioxidant present in exemplar samples with his OIT measurements. He claimed that the variation in antioxidant concentration was "significant and correlated with the variation in the OIT of the same mesh samples." However, contrary to standard practices in the scientific and engineering fields, Dr. Priddy does not present any data related to these experiments. As such, his statements cannot be critically assessed.

Additionally, Dr. Priddy's extraction method is neither referenced nor experimentally validated, which could explain why he was unable to find DLTDP in any of the samples tested. Another Plaintiffs' expert, Dr. Jordi, was able to identify DLTDP in all of the exemplar and explanted samples tested.[85] Dr. Priddy's dubious extraction technique, combined with the shortcomings of his OIT testing, renders any conclusions related to the variability of antioxidant loading levels and the efficacy of said additives under *in vivo* conditions, scientifically unreliable.

Dr. Priddy supported his opinion regarding the alleged invalidity of PROLENE as a permanently implantable material by claiming that "the antioxidants are themselves degraded over time." His basis for this statement is a study he co-authored, in which various antioxidants are intentionally oxidized using UV light or *N*-bromo, *N*'-chloro-hydantoin in methylene chloride.[182] Neither of these oxidizing media are found *in vivo*, and therefore his statement is scientifically unfounded.

In claiming that PROLENE mesh surfaces rapidly degrade and become brittle due to oxidation, Dr. Priddy referenced work published by Leibert, which was discussed earlier in this report.[57] However, Liebert concluded the opposite of what Dr. Priddy stated, "[i]nfrared spectra and

[182] Bell, B., Beyer, D.E., Maecker, N.L., Papenfus, R.R., and Priddy, D.B., 1994, Permanence of polymer stabilizers in hostile environments: *Journal of Applied Polymer Science*, v. 54, no. 11, p. 1605–1612.

mechanical testing of implanted and non-implanted filaments containing an antioxidant show no changes in chemical or physical properties as a result of implantation."

Dr. Priddy's report contained numerous statements that either lack the specificity required to conclude that it applies to PROLENE mesh, were unfounded based on the scientific literature or lack thereof, or both. For example, his opinion that PROLENE cannot withstand decades-long exposure to a hypothetical situation containing four criteria is both generalized and unfounded. He failed to specify how large the surface area of the mesh needs to be, and how much oxygen content is needed in the medium for degradation to occur. In addition, he failed to provide critical stress levels that PROLENE mesh may experience, while also failing to provide any literature supporting his accusation that this negatively impacts PROLENE's *in vivo* performance.

In his conclusion, Dr. Priddy made the unfounded statement that PROLENE "mesh will rapidly lose its strength as the polymer chains disentangle when the mesh is placed under mechanical stress." However, nowhere did he specify the applied *in vivo* stress on the mesh or the failure stress for PROLENE mesh, nor did he cite any instances of failure occurring with any mesh, let alone PROLENE.

Guelcher

Exponent reviewed the reports authored by Dr. Scott Guelcher[183,184,185] and disagrees with several of his opinions. In these reports, Dr. Guelcher did not perform any experiments, but instead relied on a small-scale study he previously conducted, and others' studies to form his opinions. In particular, he relies on the works of Talley,[66] Liebert,[57] Fayolle,[186] and Oswald.[187]

[183] Guelcher Wave 1 Report.

[184] Guelcher MDL Consolidated Case Report dated 8-24-15.

[185] Guelcher Wave 5 Cases Report.

[186] Fayolle, B., Audouin, L., Verdu, J. "Oxidation Induced Embrittlement in Polypropylene — a Tensile Testing Study." *Polym. Degrad. Stab.*, (2000) 70(3):333–340.

Dr. Guelcher equated the observed cracked layer covering the exterior of the explanted PROLENE mesh fibers with embrittlement and degradation. When referencing Ethicon's internal documents he stated, "[t]hese documents report evidence of chronic inflammation, oxidation, and degradation (referred to as micro-cracking in the Ethicon documents) of Prolene sutures,"[188] when in fact, micro-cracking and degradation should not be treated as synonyms. Without supporting his accusation of *in vivo* embrittlement with chemical or physical data, he ignored the possibility that the cracked outer layer is a material other than oxidized PROLENE.

Dr. Guelcher correctly pointed out that in a study by Fayolle[186] on thermal oxidation of polypropylene films, a reduction in the elongation at break was observed after only 150 hours of aging while an increase in carbonyl and hydroxyl concentration was detected after 250 hours (induction time). It was also shown that the polypropylene films demonstrated reduced molecular weight after approximately 150 hours. These results demonstrate that when polypropylene is subjected to oxidative degradation the polymer's elongation at break and molecular weight should both decrease and be detectable prior to the detection of any increase in carbonyl or hydroxyl groups by FTIR. In contrast, in Ethicon's Seven Year Dog Study, Ethicon's scientists demonstrated that there was no significant difference in molecular weight of PROLENE sutures implanted for seven years compared with controls, and that the sutures demonstrated increases in elongation at break after seven years *in vivo*. These results suggest the PROLENE undergoes plasticization, not degradation. Dr. Guelcher presented no evidence that conclusively demonstrates that the observed cracking is degraded PROLENE, or that the "degradation" is detrimental to the bulk physical properties of the mesh.

Dr. Guelcher's example of degradation of poly(ether urethane)s (PEU) used as pacemaker lead insulation is not relevant to the discussion of alleged PROLENE oxidation *in vivo*. PEU and PROLENE are completely different polymers; PEU is a segmented elastomer and PROLENE is a polyolefin. Their chemical composition, polarity, polymerization chemistry, mechanical

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[187] Oswald, H. J., Turi, E. "The Deterioration of Polypropylene by Oxidative Degradation." *Polym. Eng. Sci.*, (1965) 5(3):152–158.

[188] Guelcher MDL Consolidated Case dated 8-24-15, pg 9.

properties and likely their antioxidant packages are all dissimilar. Hence, it is unreasonable to believe they would behave similarly or encounter the same failure mechanism *in vivo*. This is supported by Dr. Guelcher's own results. As mentioned previously, Dr. Guelcher attempted to simulate oxidative degradation of PROLENE using an H_2O_2 solution enriched with $CoCl_2$; however, the resulting morphology of the fiber looked nothing like PROLENE mesh explants, further emphasizing the fact that conclusions cannot be extrapolated from PEU to PROLENE.

Likewise, Dr. Guelcher included a reproduced plot from an article written by Oswald,[187] of the intrinsic viscosity of *unstabilized* (i.e. without a stabilizer) polypropylene at room temperature. The viscosity remains constant until approximately 500 days, where it starts to drop off. This plot is not relevant to PROLENE mesh because as mentioned previously, PROLENE has two different antioxidants (Santonox R and dilauralthiodipropionate) added to prevent this type of degradation behavior.

Dr. Guelcher cited Talley's study[66] to support his opinion that ROS secreted by adherent inflammatory cells could lead to polypropylene oxidization. However, as was clearly addressed in the rebuttal section to the Talley's article earlier, Talley's analysis of the FTIR and XPS results were dubious given the multitude of factors that could confound data interpretation. Specifically, the likely confusion of signals in the FTIR data from water as oxidized polypropylene, the subtle nature of the bands in the FTIR spectra and the required manual baseline correction rendered the data interpretation unreliable. Furthermore, given the surface-sensitivity of the XPS technique, oxygen detected on the polypropylene explants could have resulted from multiple sources of oxygen-containing molecules, including those native to the *in vivo* environment. Talley also did not provide a clear description of how the explants were cleaned prior to analysis.

Dr. Guelcher criticized Thames' cleaning procedure stating that "sonication for long periods of time… can remove all detachable materials non-specifically"[189] and that this non-selective

[189] Guelcher Wave 5 Cases Report, pg 12.

sonication "debrides the surface of the PP fiber and removes all adherent material, including adsorbed proteins and oxidized PP."[190] However, Dr. Guelcher's comments were speculative as they were unsupported by any scientific evidence. Contrary to Dr. Guelcher's speculation, Thames has provided evidence that the removed layer was indeed biological in nature. First, Thames noted that the cleaned PROLENE explants exhibited extrusion lines that are characteristic of polymer fiber manufacturing. The extrusion lines on the cleaned PROLENE fibers were consistent with those observed on exemplar fibers. If the surface of the fibers had been oxidized and non-selectively removed by sonication as suggested by Dr. Guelcher, these fibers would not have exhibited extrusion lines that are native to freshly manufactured fibers. Second, Thames noted that cracked/flaking material was clear or translucent regardless of whether it was on clear or blue-colored fibers. This observation is critical because if the cracked material was indeed oxidized PROLENE, then flakes from blue-colored fibers would be blue instead of clear/translucent. Similar to Dr. Mays, Dr. Guelcher is silent on these relevant observations.

Dr. Guelcher also asserted that "Thames *et al.* cannot exclude the possibility that the cracked surface layer was composed of a complex mixture of oxidized PP and protein"[191] due to the peak around 1650 cm^{-1} observed in the FTIR spectrum of the surface of the explant before cleaning. Dr. Guelcher further claimed that this peak disappeared from the FTIR spectrum after Step #8 of the Thames' cleaning protocol. In fact, Thames performed material characterization of the explant after each sequence of the 5-sequence cleaning protocol. Specifically, the peak around 1650 cm^{-1} was largely reduced in the spectrum after the first sequence of cleaning, which corresponds to Step #6 prior to any sonication. As a result, it was reasonable to attribute this peak to proteins (amide I peak in IR spectrum) and other biological materials.

Although Dr. Guelcher correctly pointed out that various crosshead displacement speeds are listed in the protocols developed by Ethicon prior to the experiments, he neglected to carefully

[190] Guelcher Wave 5 Cases Report, pg 13.

[191] Guelcher Wave 5 Cases Report, pg 13.

examine Ethicon's study reports, where the actual crosshead displacement rate was consistently recorded as 1 in/min on the same page as the test data for each testing time point.[192] In fact, the 7 year test report emphasized that "[s]even year testing conditions were based on the one year and two year data to keep them consistent throughout this study."[193]

Dr. Guelcher opined that "the presence of antioxidants does not permanently protect the TVT mesh against degradation, and thus it is not possible to guarantee that it will perform its intended function after implantation."[194] However, he failed to produce or cite any literature or testing that supports his opinion that the overall intended function of the mesh has been compromised or that it suffers from a depletion of antioxidants. This statement ignored Dr. Jordi's finding in his expert report on the Bellew v. Ethicon matter that antioxidants remain in explanted PROLENE mesh even after storage in formalin, which was shown to extract Santonox R from PROLENE.[195]

Dr. Guelcher went on to claim that the "effects of oxidation on the stability of PROLENE were known to Ethicon prior to launching TVT, but the company did not consider the risks associated with polypropylene oxidation on the stability of the TVT mesh." This statement completely ignored the years of research conducted at Ethicon into the safety and efficacy of PROLENE. In fact, the development of the TVT device leveraged work on the raw material, PROLENE resin, which began as early as the mid-1960s.[20] Ethicon was active in "considering" the risks involved in this device, and after consideration of these risks Ethicon (and the FDA) determined it was sufficiently safe and effective to market.

Dr. Guelcher further quoted Dr. Peter Moy's November 5, 1984 report to support his claim that "treatment with 30% hydrogen peroxide caused oxidation of the PP suture (as reported by Dr. Moy), then ROS secreted by adherent macrophages would also be expected to cause

[192] ETH.MESH.11336087, ETH.MESH.11336182

[193] ETH.MESH.11336181

[194] Guelcher MDL Consolidated Case Report dated 8-24-15, pg 8.

[195] Jordi Bellew Report dated 7-7-14, pg 73-74.

oxidation."[196] However, Dr. Guelcher has clearly misinterpreted the intent and limited utility of Dr. Moy's study. As an attempt to replicate the transverse cracks observed on PROLENE explants, PROLENE sutures were incubated with 30% hydrogen peroxide for a year at room temperature. These sutures did not exhibit any visible surface cracks despite the oxidative strength of the peroxide solution. Dr. Moy stated, "Infrared spectroscopic examination of PROLENE explants however do show the presence of oxidative end products. While the combination of a proportionally small but severely oxidized surface and an unaffected core has *not* (emphasis added) been duplicated in laboratory oxidation studies, the possibility of a highly specific in-vivo oxidation process remains."[197] Contrary to Dr. Guelcher's claim, Dr. Moy did not indicate that the infrared spectroscopy analysis of the peroxide-treated samples "revealed evidence of oxidation products,"[198] Moreover, Dr. Moy never stated that a 30% peroxide solution can be used to replicate the *in vivo* environment. Although Dr. Moy suggested that infrared spectroscopic examination of PROLENE explants showed the presence of oxidative products, as mentioned in the "Microcrack Committee Investigation" section above, interpreting the FTIR spectra obtained by Ethicon is non-trivial due to a multitude of factors. Specifically, the antioxidant used in PROLENE, cross-linked proteins, fatty acid esters as well as oxidized PP could all have given rise to absorption peaks between 1650 and 1810 cm^{-1}.

Dr. Guelcher continued stating that Costello[50,199] reported polypropylene mesh oxidation and embrittlement; the conclusions were drawn by comparing pristine and explanted meshes via molecular weight, SEM imaging, and compliance testing. This is simply incorrect; Costello never reported the molecular weight of either pristine material or explanted material in either of the two articles cited by Dr. Guelcher. As discussed previously, Costello's pseudo-compliance testing methodology is flawed and contradicts Ethicon's testing results in the Seven Year Dog

[196] Guelcher Wave 5 Cases Report, pg 18.

[197] ETH.MESH.15958454

[198] Guelcher Wave 5 Cases Report, pg 18.

[199] Costello, C. R., Bachman, S. L., Grant, S. A., Cleveland, D. S., et al. "Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants From a Single Patient." *Surg. Innov.*, (2007) 14(3):168–176.

study. Furthermore, while the SEM images presented by Costello show the presence of transverse cracking, no work was done to identify the elemental composition of the layer, thereby not confirming the cracked surface is indeed oxidatively degraded PROLENE instead of a remnant biological material.

Finally, Dr. Guelcher asserted that polypropylene mesh samples in a rat abdominal wall model were associated with more adherent inflammatory cells as compared to polypropylene sutures, suggesting that the form factor and density of fibers could lead to different degrees of foreign body response and the resulting oxidative degradation. However, while the extent of foreign body response may be different towards various suture or mesh products, there is no evidence to ascribe that purported, disparate foreign body response to oxidative degradation of Ethicon's meshes. As demonstrated in the Thames study,[86] 75 explants of various device types, after an implantation duration of 0.1 – 10 years, were found to be free of oxidative degradation. Furthermore, these mesh explant samples were stored in fixative for various durations, ranging from 0.1 to several years. As mentioned previously, the effectively cleaned explants exhibited extrusion lines similar to those on exemplar mesh fibers, indicating that the explants were not oxidized or degraded. This result was also supported by Thames' FTIR analysis.

Dunn

Exponent has reviewed the January 23, 2016 and August 23, 2016 expert reports of Dr. Russell Dunn relevant to this litigation.[200] In forming his opinions, Dr. Dunn has relied on published literature, produced documents, and testing. Dr. Dunn begins his reports with a broad overview of polymers, PP and PROLENE. In general, Dr. Dunn's explanations and descriptions of polymers, PP and PROLENE are consistent with polymer science fundamentals. However, as Dr. Dunn moves into discussion of oxidation, his statements become both overly broad and misleading.

[200] Expert report of Russell Dunn, dated January 23, 2016; Expert report of Russell Dunn, dated August 23, 2016.

In reviewing the various ways in which PP can oxidize, Dr. Dunn never settles on a method that actually occurs *in vivo*. For example, Dr. Dunn discusses possible oxidation pathways using reactive oxidative species (ROS), such as hydrogen peroxide allegedly causing oxidation of the mesh, but then moves on to discuss the antioxidant package within Ethicon's PROLENE and how it could be depleted due to thermal conditions. This lack of consistency or clear thesis on the alleged oxidation method suggests that Dr. Dunn does not have a realistic or substantiated theory of *in vivo* mesh oxidation.

Dr. Dunn also states that "[t]he oxidative behavior of PP described is independent of whether the polypropylene product is a medical device or a non-medical device."[201] This statement is misleading as it implies that the material will react in exactly the same manner regardless of exposure conditions. In fact, the oxidative behavior of PP is almost completely condition dependent. While the mechanism of PP oxidation is the same regardless of physical location, the propensity of a material to undergo oxidation is condition specific, which is vastly different inside or outside the body.

Next, Dr. Dunn discusses the additive package used to stabilize and color PROLENE. Dr. Dunn references a study of long term thermal stability[202] that he claims "determined the correct proportion of these two antioxidants."[203] He also includes a figure from the study that displays PP "time to embrittlement" as a function of the concentration of antioxidants DLTDP and 2,2'-methylenebis[6-(1-methylcyclohexyl-*p*-cresol)] (MCPC).[204]

Dr. Dunn's statements and conclusions regarding the PROLENE antioxidant package include a number of errors or omissions. First, Dr. Dunn cites a study for a different additive package than used in PROLENE and uses it to support his opinion that the ratios of the two antioxidants "are not in an optimal concentration in the Prolene material."[204] Although MCPC and Santonox R are

[201] Expert report of Russell Dunn, dated January 23, 2016, pg 7.

[202] Brydson, J.A. *Plastics materials*. Butterworth-Heinemann, 1999, p. 261.

[203] Expert report of Russell Dunn, August 23, 2016, pg 17.

[204] Expert report of Russell Dunn, dated January 23, 2016, pg 10 – 11; Expert report of Russell Dunn, August 23, 2016, pg 17.

both phenol-based antioxidants, they are different compounds and are expected to exhibit different properties and performance in this application. For example, antioxidant efficiency is known to depend on the solubility and diffusion coefficient of a given antioxidant in PP.[205] Dr. Dunn opines that "normalization" allows him to label embrittlement time data as though it applied to PROLENE, even though embrittlement time was measured for a different stabilizer system. The performance of a stabilizer system subjected to long term thermal stability testing depends upon multiple factors including the additive concentrations and combinations, sample dimensions, and test temperature.[206] Santonox R and MCPC have different sizes and chemical structures and, therefore, will differ in their efficiency. Due to the difference in molecular weight between MCPC and Santonox R, the MCPC concentrations reported in the study cited by Dr. Dunn cannot be used for direct comparison to Santonox R.[207] Hence, Dr. Dunn has not provided evidence to support his claim that the PROLENE stabilizer system is "not optimal."

In his August 23, 2016 report, Dr. Dunn used the work of Liebert *et al.*,[57] which I have summarized in the above literature section, to support some of his conclusions. However, Dr. Dunn's review of Liebert *et al.* misrepresents the results presented by the researchers. Regarding mesh implants, Dr. Dunn described Liebert *et al.* as reporting "rapid oxidation of these implants in hamsters."[208] This is a misstatement of the Liebert paper as it reported that while non-antioxidant stabilized was shown by FTIR to be oxidized, PP stabilized with antioxidants did not show any indication of degradation.

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[205] Bart, J.C., *Polymer additive analytics: industrial practice and case studies (Vol. 14)*. Firenze University Press, 2006, p. 105.

[206] Zweifel, H., Maier, R.D., Schiller, M. and Amos, S.E. *Plastics additives handbook*. Hanser Gardner, 2009, p. 49.

[207] The molecular weight of Santonox R (358.5 g/mol) is ~15% lower than that of MCPC (420.6 g/mol). Although both compounds contain two phenol groups per mole, the difference in molecular weight means that MCPC has a 15% lower phenol content than Santonox R (i.e., 4.8 moles phenol per kg for MCPC versus 5.6 moles phenol per kg for Santonox R). (NIST chemistry webbook page for MCPC, accessed 12/1/2016, available at: http://webbook.nist.gov/cgi/cbook.cgi?ID=77-62-3&Units=SI; NIST chemistry webbook page for Santonox R, accessed 12/1/2016, available at: http://webbook.nist.gov/cgi/cbook.cgi?ID=C96695&Mask=80).

[208] Expert report of Russell Dunn, dated August 23, 2016, pg. 23.

In addition, Dr. Dunn discusses the use of failure analysis as a tool for polymer scientists, including the use of such a tool on polymers that are used in medical devices[209] As a reference, Dr. Dunn cites a volume of the ASM Handbook pertaining to plastic failure characterization, and highlights a figure from that reference outlining the "specific steps" that should be followed when conducting polymer failure analysis.[210] While Dr. Dunn takes the time to emphasize the prudent use of microscopic, chemical, and thermal methods in polymer failure analysis, he is notably and completely silent on the portion of the referenced handbook that teaches the use of mechanical testing and molecular weight evaluations.[211] If Dr. Dunn were to remain true to the spirit and teachings of his own references, he would be forced to acknowledge the mechanical testing and molecular weight testing performed by Ethicon which unequivocally confirms a lack of embrittlement and a lack of degradation of PROLENE during implantation. For example, Dr. Dunn summarized some of the findings of Ethicon's scientists with regards to the observed surface cracking on explanted PROLENE sutures. In citing the Seven Year Dog Study, Dr. Dunn reports the surface cracking observed on the explanted sutures, yet fails to mention that all explanted PROLENE sutures showed a significant increase in their elongation at break (degree of stretching before breaking) compared to controls. Polymers, including PP-based PROLENE, that suffer from cracking and oxidative degradation should not and do not exhibit an *increase* in their ability to stretch. From a polymer science perspective, the exact opposite behavior is expected. It is worth noting that Dr. Dunn offers no scientific explanation as to why his opinions regarding *in vivo* cracking and oxidation of PROLENE do not reconcile with Ethicon's elongation at break data or well-established structure-property relationships for polymeric materials.

Dr. Dunn also performed an examination of exemplar Ethicon TVT mesh using visual and microscopic analysis, followed by FTIR and XPS analysis.[212] The same mesh was then exposed to an *in vitro* oxidizing medium, after which it was evaluated using SEM, FTIR, and XPS.

[209] Expert report of Russell Dunn, dated January 23, 2016, pg 12.

[210] Expert report of Russell Dunn, dated January 23, 2016, pg 12 – 13.

[211] Expert report of Russell Dunn, dated January 23, 2016, pg 12 – 14.

[212] Expert Report of Russell Dunn, dated August 23, 2016, pg. 51 – 68.

Unstabilized PP pellets were used as a control before and after exposure to the same oxidizing medium, and were analyzed with FTIR and XPS. Dr. Dunn's experiment shows the intentionally oxidized PROLENE filaments have a distinct appearance under SEM when compared to other studies,[213] while the FTIR spectra show the expected signatures for an oxidized PP-based material, they do not provide any evidence that PROLENE oxidizes *in vivo*.

Klinge

Exponent reviewed the report authored by Dr. Uwe Klinge[214,215,216] and disagrees with several of his opinions. In this report, Dr. Klinge did not perform any experiments to support his claims of *in vivo* degradation of PROLENE, but instead relied on others' studies to form his opinions. In particular, he relies on the works of Liebert,[57] Costello,[50] Cozad,[53] and Clavé[45] as well as Ethicon's Seven Year Dog Study,[51] all of which have been previously discussed in detail.

Dr. Klinge opined that antioxidants, DLTDP and Santonox R, leach from PROLENE with time *in vivo*, but failed to perform his own experiments and instead relied on a study presented in an expert report authored by Dr. Jordi in 2013.[217] In this study, Dr. Jordi used liquid chromatography-mass spectrometry (LC-MS) to attempt to show that antioxidants can leach from PROLENE. LC-MS is an experimental technique that, when correctly employed, can be utilized to determine the concentration of various extractable components in a polymer. Dr. Jordi performed this analysis on explants as well as on various control samples in an attempt to determine the concentrations of DLTDP and Santonox R in each specimen. In this study, during sample preparation, Dr. Jordi attempted to mechanically remove attached biological material using forceps, however, complete tissue removal was never confirmed prior to his LC-MS analysis. Dr. Jordi then made *quantitative* conclusions on the amount of antioxidants in the

[213] Expert Report of Russell Dunn, dated August 23, 2016, pg. 60.
[214] Klinge Wave 1 POP Report dated 11-17-15.
[215] Klinge Wave 1 SUI Report dated 11-16-15.
[216] Klinge ETH MDL Consolidated Case Report dated 8-24-15.
[217] Jordi Lewis Report dated 10-12-13.

explanted mesh based on the original mass of the specimen. Without verifying that the measured mass is solely from the mesh and not in part from residual biologic material, any conclusions regarding the levels of antioxidants DLTDP and Santonox R present are erroneous. Furthermore, Dr. Jordi's control experiments leave much to be desired. His formalin-treated mesh controls were only exposed for a fraction of the length of time the explants were exposed to formalin. As a result, this control is invalid and it is impossible to eliminate the possibility that Santonox R and DLTDP were drawn out of the explants during their extended storage in formalin. In fact, Dr. Jordi showed in his analysis that Santonox R is easily extracted from PROLENE after exposure to formalin for only 48 hours at 60°C. Therefore, any conclusions relating to the concentration of antioxidants in explanted mesh while *in vivo* based on Dr. Jordi's LC-MS data are unfounded.

Michaels

Exponent reviewed the report authored by Dr. Paul Michaels[218] and disagrees with several of the findings and conclusions. Dr. Michaels, a medical doctor, did not perform any testing to characterize "the cracked and degraded surface layer,"[219] but instead relied on others' studies to support his opinion of *in vivo* oxidative degradation of PROLENE mesh. In particular, he cites studies which have been previously discussed in detail such as Liebert,[57] Mary,[58] Costello,[50] Clavé,[45] and Ethicon's internal studies.[220]

[218] Michaels expert report dated 7-1-16.

[219] Michaels expert report dated 7-1-16, pg 6.

[220] ETH.MESH.15955438, ETH.MESH.1595540, ETH.MESH.15955463, ETH.MESH.13334286, ETH.MESH.15955462.

Conclusion and Opinions

Based on my analysis, as well as my education, training, and experience in mechanics of materials, polymer science, materials chemistry, and mechanical engineering, I have formed the following opinions to a reasonable degree of engineering and scientific certainty. If additional information becomes available, I reserve the right to supplement or amend any or all of these opinions.

- Based on the tensile testing performed by Ethicon during its Seven Year Dog Study, it has been conclusively determined that the PROLENE material becomes more ductile, tougher, and less stiff while implanted.

- Based on the molecular weight analyses performed by Ethicon during the seven year dog study, the PROLENE material is not suffering from any quantifiable degradation while *in vivo*.

- Based on its historical use, long-term testing performed by Ethicon, and retention of bulk physical properties while *in vivo*, PROLENE is a suitable material for implanted mesh devices.

- No reliable scientific evidence has been presented to decisively determine that the "bark layer" is comprised of PROLENE. H&E staining, polarized light microscopy, and melting point analysis are not accepted methods used in the conclusive chemical identification of polypropylene-based materials.

- Plaintiffs' experts' assertion that the PROLENE mesh material has degraded *in vivo* is based solely on an observed reduction in melting point as well as visual and microscopic observations of "bark micro-cracking," which is contrary to scientific principles.

- Plaintiffs' experts' assertion that the PROLENE mesh material has become brittle is also solely based on visual and microscopic observations of "bark micro-cracking," not on mechanical testing, and is contrary to the scientific findings from Ethicon's Seven Year Dog Study.

- Plaintiffs' experts' assertion that PROLENE becomes stiffer (less pliable) and resists tissue contraction causing inflammation/pain is based on observed "bark micro-cracking" and tactile feel (a highly subjective assessment). No standardized mechanical testing has been performed to support this subjective assertion. This assertion is contradicted by the mechanical property testing performed by Ethicon, and the fundamental principles of mechanics of materials.

- The images presented in the Plaintiffs' expert report[221] of "freshly excised" cracked PROLENE mesh that has reportedly never been exposed to formalin need to be tempered with Ethicon's findings that exposure to air alone can cause a saline-preserved "wet" explanted fiber to crack in a relatively short period of time. Moreover, the possibility cannot be excluded that mechanical forces applied to the mesh during explantation did not contribute, and/or cause the observed cracking.

- There has been no testing performed or scientific literature cited to support the belief that degraded PROLENE is capable of being histologically stained with H&E stain. Therefore, any related conclusions, are scientifically unreliable.

- Dr. Iakovlev has not used any reliable scientific methods to conclusively determine that an outer oxidized PROLENE layer stains when exposed to H&E. Dr. Iakovlev's assertion that the PROLENE mesh material has degraded *in vivo* is based solely on visual and microscopic observations of "bark" microcracking. He has conducted no

[221] Iakovlev MDL Consolidated Case Report dated 8-24-15, pg 83-84.

quantitative experiments to confirm his visually based allegation that the mesh material is degraded or oxidized.

- Dr. Iakovlev has not performed any control experiments nor cited any scientific studies that support his belief that degraded PROLENE is capable of being histologically stained with H&E stains, and for these reasons, his conclusions are flawed and suspect.

- Through a series of controlled oxidation, microtoming, and microscopy experiments, Exponent demonstrated that oxidized PROLENE mesh fibers and sutures do not become stained with H&E dyes. This fact is supported by polymer science first principles, given that PROLENE does not possess chemical groups amenable to binding with the H&E stain molecules.

- Artifacts can be easily introduced during sample preparation, sectioning, staining, and imaging, giving the appearance of darkened outer layers.

- A brittle outer layer will not contribute to the stiffness of the mesh if it is thin, cracked, and discontinuous. Dr. Iakovlev's opinion that a thin, cracked, porous outer layer causes an increase in mesh stiffness is not consistent with first principles of polymer science and contradicted by the measured modulus data from Ethicon's seven year dog study.

- Upon thorough cleaning, the presence of extrusion die lines underneath the crust layer of explanted mesh has been confirmed. Had the original fiber surface suffered from *in vivo* oxidation and formed an outer crust layer, die lines would not exist after cleaning.

- Based on the microscopic examination of intentionally oxidized mesh after cleaning, the cleaning process does not remove oxidized material from the surface of the PROLENE mesh.

- Biological elements, native to the *in vivo* environment and foreign to the PROLENE resin formulation, were conclusively identified within the crust layer of explanted mesh. As such, the crust is biological in nature and not degraded PROLENE.

If you have any questions or require additional information, please do not hesitate to contact me.

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